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Hyalinization of the Seminiferous Tubules Associated with Normal or Failing Leydig-Cell Function. Discussion of Relationship to Eunuchoidism, Gynecomastia, Elevated Gonadotrophins, Depressed 17-Ketosteroids and Estrogens[1,2]

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HYPOGONADISM in males may be due to a primary defect of the testis or of its constituent parts; it may likewise be secondary to failure of one or more hormones of the anterior pituitary. Therefore the determination of the primary factor in testicular failure (and the determination of the secondary effect upon the other endocrine glands) becomes of utmost importance in the selection of a rational therapeutic approach. To this end we have attempted to categorize instances of male hypogonadism: first, by separating those cases in which failure occurred during adulthood, for example, the male climacteric (1), from those in which failure occurred at or before-puberty; second, by subdividing the prepuberal-failure group into their constituent sub-groups or syndromes. We have already described a syndrome in which both the hor-

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TABLE 1. CLINICAL FEATURES OF 20 CASES OF PREPUBERAL HYALINIZATION OF THE SEMINIFEROUS TUBULES WITH PARTIAL OR COMPLETE FAILURE OF LEYDIG-CELL FUNCTION

Clinical Subdivision	Eunuchoidal					Moderately Eunuchoidal				
Case No.	1	2	3	4	5	6	7	8	9	10
Age, yr.	25	18	55	27	18	19	20	19	69	22
Weight, lb.	117	213	107	144	152	125	145	131	157	153
Height, in.	73.5	70	68.25	72.75	67.25	72	73	68.25	65.5	72.3
Span, in.	73	74	76	73	72.5	70.25	76	70.75	69.5	74.2
Sole to Sym. Pub., in.	39	38.75	37.25	38	36.5	37.5	38.5	37.25	35.5	37.5
Pub. Sym. to Vertex, in.	34.5	31.25	31	34.75	30.75	34.25	34.5	31	30	35
Voice Pitch	High	High	Normal	Normal "cracks"	Normal	Husky	Husky	Normal	Normal	Normal
Recession Scalp Hair	None	None	None	Slight	Slight	Slight	None	Slight	Bald	Moderate
Facial Hair	None	None	None	None	None	None	None	None	Normal	Chin, upper lip
Axillary Hair	None	None	Sparse	Normal	Normal	Sparse	Normal	Normal	Normal	Normal
Body Hair	None	None	None	None	None	None	None	None	None	None
Pubic Hair, Distribution	Female	Sparse female	Female	Female	Female	Female	Female	Male	Female	Female
Hair, Extremities	None	Slight	None	Ankles only	Sparse forearms & legs only	Forearms & legs only	None	Legs only	None	Normal
Gynecomastia, Degree	0	++++ (fat)	0	+	±	+	+	+	++++	0
Gynecomastia, Duration, yrs.	—	4	—	11	—	3	5	3	Many years	—
Penis Length, in.	1.5	1.5	3.5	3	2.75	3.75	2.75	3.5	3.5	1.5
Penis Diameter	Thin	Thin	Thin	Normal	Thin	Normal	Normal	Normal	Normal	Normal
Erection	Seldom	At will	At will[1]	At will	At will	At will	Occ.	At will	At will[1]	At will
Ejaculation	Never	Never	Normal	None in 10 yrs.	+	+	+	+	+	+
Seminal Fluid, Amount, cc.	After Rx 0.5	—	None for 6 mos.	—	Could not collect	0.5	—	2.5	—	1
Seminal Fluid, Sperm	After Rx 0	—	—	—		0	—	0	—	0
Testis Size, Gross, cm	1½×1×1	Lima bean	Pea	Pea	Lima bean	1½×1×1 lima bean	Large almond	Lima bean	1½×1×1	Rt.—small white grape Lf.—pea
Bone Age		Normal	Normal	Delayed	Normal	Normal	—	—	Normal	Normal

Clinical Subdivision	Moderately Eunuchoidal						Normal			
Case No.	11	12	13	14	15	16	17	18	19	20
Age, yr.	18	22	19	27	19	22	18	25	21	32
Weight, lb.	123	144	125	100	137	160	210	239	165	226
Height, in.	70.5	74.5	68	66	76	75	67.75	73	62	68.25
Span, in.	68.75	76	68.5	66.5	77	75	69.5	72.25	62	65.25
Sole to Sym. Pub., in.	37.25	38.75	35.75	34.5	39	40.25	35	38	31	32.75
Pub. Sym. to Vertex, in.	33.25	35.75	32.25	32.5	37	34.75	32.75	35	31	35.5
Voice Pitch	Normal	Normal	Normal	High normal	Normal	Normal	Normal	Normal	Normal[1] high	Normal
Recession Scalp Hair	Moderate	Moderate	Slight	Slight	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Facial Hair	None	Sideburns, chin	Sideburns	Chin, cheeks, upper lip	None	None	None	Chin, sideburns	Chin, sideburns	Normal
Axillary Hair	Normal	Normal	Normal	Normal	Normal	Sparse	Normal	Normal	Normal	Normal
Body Hair	None	None	None	None	None	None	None	None	None	Normal
Pubic Hair, Distribution	Female	Male	Male	Sparse male	Male	Male	Male	Female	Female	Male
Hair, Extremities	Forearms & legs	Normal	Normal	None	Normal	Normal	Normal	Normal	Normal	Normal
Gynecomastia, Degree	++	0	0	0	+	0	++++	++++	++++	++++
Gynecomastia, Duration, yrs.	3	—	—	—	4	—	2	11	5	18
Penis Length, in.	2.5	3.75	3.5	3.5	3	3	1-hypospadias	2.5	2.5	2.5
Penis Diameter	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Erection	At will	At will	At will	At will[1]	At will	At will	At will	At will	At will	At will
Ejaculation	+	+	+	+	+	+	+	+	+	+
Seminal Fluid, Amount,	0.5	3	2	0.5	1	3	—	2	0.5	0.5
Seminal Fluid, Sperm	0	0	0	0	0	0	—	0	0	0
Testis Size, Gross, cm.	Pea	Pea	Lima bean	1½×1×1	1½×1×1 ¾×⅞×⅞	Lima bean	Rt.—pea Lf.—small almond	Lima bean	Lima bean	Lima bean.
Bone Age	Normal	—	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal

[1] * indicates recent loss of potentia associated with symptoms of the male climacteric.

monal and gametogenic functions of the testis have failed, i.e., functional prepuberal castration in males (2).

Recently Klinefelter, Reifenstein and Albright (3) have lucidly described a new syndrome in which the main pathology of the testis was hyalinization of the seminiferous tubules. In the present communication we shall discuss the association of seminiferous tubule failure with: 1) normal-appearing Leydig cells accompanied by normal hormonal function of the testes and 2) abnormal-appearing Leydig cells accompanied by evidence of partial failure of hormonal function. The dichotomy between failure of one portion of the testis without failure of the other portion is understandable when one remembers that the seminiferous tubules are concerned with the formation of germ cells, while the Leydig cells constitute an organ of internal secretion which could as effectively be located at some distant site. It is true that the maintenance of the seminiferous tubules is in part dependent upon testicular secretion. However, the relationships of the pituitary to the gametogenic and hormonal portions of the testis are regarded as separate and distinct functions. The gametogenic principle of the anterior pituitary is commonly called follicle-stimulating hormone (F.S.H.) because of its action upon ovaries. In the female, purified F.S.H. stimulates follicular growth but does *not* cause secretion of estrogen; and simiarly in the male F.S.H. stimulates spermatogenesis, but does not cause secretion of androgen (4). The interstitial-cell-stimulating hormone (I.C.S.H.) of the anterior pituitary is commonly called luteinizing hormone (L.H.) because of its action upon ovaries. In the female I.C.S.H. stimulates the interstitial or thecal cells and in combination with F.S.H. causes secretion of estrogen. In the male I.C.S.H. stimulates the interstitial cells of Leydig to secrete androgen. This androgen is excreted in a form that, along with certain adrenal steroids, can be measured colorimetrically as 17-ketosteroids. F.S.H. and I.C.S.H. are excreted in the urine and are measured together, biologically, as gonadotrophins.

FEATURES OF THE SYNDROME

A. *Constant features.* A case, to be admitted to the present category, must have the following features, which are invariably present in all instances of the syndrome:

1. *Small testes* that vary in size from that of a small pea to that of a small white grape. The usual measurement is $1\frac{1}{2} \times 1 \times 1$ cm. a) Biopsy of the testis must reveal hyalinization of the tunica propia of the seminiferous tubules, which is associated with failure of spermatogenesis. Usually the only identifiable cell in the seminiferous tubules is the supporting cell of Sertoli. b) Leydig cells are always present and occur in clumps of various sizes.

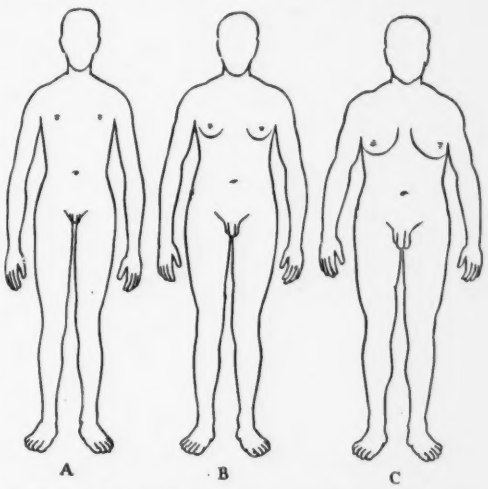

Chart 1. Schematic drawing representing the body configuration, genital and breast development of the three groups comprising the syndrome. Note the absence of gynecomastia and the under-developed genitalia in the eunuchoidal group (A); the greater development of each in the moderately eunuchoidal group (B); the association of marked gynecomastia and normal genital development in the normal group (C).

2. *Azoöspermia* occurs in all cases in which ejaculation is possible.

3. *High gonadotrophins.* Urinary gonadotrophins are always markedly elevated above normal levels.

B. *Variable features.* All cases admitted to the category have deviations from normal in one or more of the following features (all deviations, however, are not invariably present in all cases):

1. *Skeleton.* Stature may be tall or short. The skeletal proportions range in type from entirely normal to decidedly eunuchoidal (table 1, chart 1). The bone age may be normal or there may be delay in osseous development.

2. *Gynecomastia.* Clinically the mammary

area may be normal, or bilateral increases in amount of palpable breast tissue and in the size of nipples and areolae may be encountered. When gynecomastia is present, onset of the enlargement occurs at puberty and continues progressively for several years, thereafter becoming stationary. Microscopically normal or unusual development of the ducts, alveoli or connective tissue may occur. In those cases in which other signs of eunuchoidism are few or absent, gynecomastia seems to be a constant feature (table 1 and chart 1).

3. *External genitalia.* The size and development of the penis and scrotum vary from normal to completely infantile. As in other types of eunuchoidism and in castrates, erections occurred in all cases.

4. *Hair distribution.* Scalp hair may show lack of recession or may exhibit normal recession. Pubic hair pattern may vary from sparse female to normal male. Axillary, body and extremity hair may be absent, sparse or normal. Facial hair varies from abundant to absent.

5. *Pitch of voice* varies from that of a normal adult male to that of a prepuberal child.

6. *Muscular development and strength* vary from normal to very poor.

7. *Leydig-cell appearance.* The quality of the Leydig cells may vary from normal to poor as judged by their histological appearance.

8. *Excretion of 17-ketosteroids* may vary from normal to very low.

9. *Excretion of estrogens* may vary from normal to low, but is never increased in amount.

SUBDIVISION OF THE SYNDROME

A patient who is admitted to the category because he has the constant features of the syndrome may be further classified into one of the following three subdivisions on the basis of the number and extent of the variable features. The three subdivisions are eunuchoidal, moderately eunuchoidal and normal.

The eunuchoidal group included those patients who had eunuchoidal skeletal proportions, marked delay in development of male hair pattern, poor muscular development, low 17-ketosteroid excretion, the least gynecomastia, the least development of external genitalia, and an inability to have ejaculations.

The moderately eunuchoidal group included patients with eunuchoidal skeletal proportions associated with slight delay in development of male hair pattern and fair muscular development.

The normal group included patients with approximately normal skeletal proportions, normal or slight delay in hair pattern development and striking gynecomastia. These patients had normal 17-ketosteroid excretion, normal external genitalia, normal ejaculations, and normal muscular development. However, each subject exhibited some tendency to deviate from complete normality.

METHODS

Gonadotrophins were concentrated from 12-hour overnight urine specimens, using the alcohol precipitation, dialysis, alcohol reprecipitation method described by Heller and Chandler (5). The concentrate from the entire 12-hour urine specimen was injected into a single rat as previously indicated (2, 6). Results are expressed directly in terms of recipient immature-rat ovarian weights.

The 17-ketosteroids were determined from an aliquot of the 12-hour overnight specimen. Urines were extracted with CCl_4 by shaking. The Holtorff-Koch (7) modification of the Zimmerman reaction was used for color development. No color correction factor was used.

Estrogens were separated from 12-hour specimens by extraction in a Wolfe-Hirshberg continuous extractor. The extracts were assayed by dividing and injecting $\frac{1}{4}$ of the extract once daily for 3 days into each of four immature female rats. Uterine weight increase at autopsy was used as the end-point (8).

Histological technics used are described in the companion paper (9).

RESULTS

The 20 instances of the syndrome reported in this communication were assembled over the short period of one year, a fact which suggests that it occurs frequently. We have had occasion to examine or study incompletely about thirty additional cases. Only those subjects who submitted to the complete investigation are reported.

Etiology. No common etiological factor has been uncovered. Mumps during childhood oc-

curred in twelve cases—in eleven without orchitis, and in one associated with unilateral orchitis. One patient believed his testes had been normal in size until kicked by a horse. Three patients (*Cases 3, 9,* and *14*) had gonorrheal infections at ages seventeen, eighteen and thirty-nine respectively. No other factors of possible etiological significance were evident from the medical histories. The clinical features are set forth in table 1.

geneous material. A detailed microscopic description of the material is presented in the companion paper. All nineteen of the twenty cases in which testicular biopsies were taken exhibited the characteristic hyalinization and thickening of the tunica propia of the seminiferous tubules. All stages of hyalinization were encountered. This affected spermatogenesis ad-

TABLE 2. RESULTS OF HORMONE ASSAYS IN UNTREATED CASES OF HYALINIZATION OF SEMINIFEROUS TUBULES

Clinical Subdivision	Patient No.	Gonadotrophin Assays[1]—Using Immature Female Rats		17-Ketosteroids		Estrogens[4]
		No. of Assays	Ovarian Weight	No. of Assays	Mg./12 hours[3]	
			Mg.			
Eunuchoidal	1	9	96	2	3.45	Low
	2	3	78	2	6.9	Low
	3	2	105	3	3.9	Low
	4	2	50	1	0.6	—
	5	2	65	2	2.9	Low
Moderately Eunuchoidal	6	3	85	3	2.5	Low
	7	1	99	1	4.4	—
	8	1	56	—	—	—
	9	2	61	1	2.0	Normal
	10	2	81	3	2.7	—
	11	9	66	4	3.5	Low
	12	4	90	1	2.9	Low
	13	4	88	2	3.3	Normal
	14	4	73	2	6.8	Low
	15	4	103	2	4.1	Low
	16	3	104	2	4.9	Normal
Normal	17	1	56	2	3.4	Normal
	18	5	98	2	6.4	Normal
	19	9	75	5	5.0	Low
	20	4	55	2	4.0	Normal
Average		74	80.7 (35–159)	No. Cases 19	4.02 (0.6–6.9)	
Normal Men		72	12.46 (5–23.1)[2]	31	6.89 (3.1–14.0)	

[1] Gonadotrophin assays were performed upon 12-hour overnight urines. The entire concentrate from the 12-hour urine was injected into one 22–24 day old female albino rat. Maximal uterine weight stimulation and vaginal opening occurred in every assay animal and are therefore omitted from the table. Luteinization of the larger ovaries was frequently observed.
[2] Uterine weight stimulation occurred in approximately ¼ of the assays of 12-hour urine concentrate of normal men.
[3] 17-ketosteroids are expressed as mg. equivalents of androsterone.
[4] Assay end-point was the uterine weight stimulation of immature female rats.

Constant features. 1) *Small testes* were palpable in the scrotum in all twenty cases. They were decidedly firmer than normal, round or oblong in shape, and as small as a pea or as large as a small white grape. The striking feature was that the testis was smaller and of harder consistency than the epididymis, and smaller and firmer than the testis found in other types of eunuchoids that we have studied. Cut sections revealed a yellowish homoversely in each case: in some tubules evidence of incomplete spermatogenesis could be seen; other tubules were quite empty except for the presence of Sertoli cells; while the greatest number of tubules in all cases showed complete obliteration of the lumen. The interstitial cells of Leydig were much more numerous per unit area than is ordinarily the case for normal testes, and in each instance were arranged in clumps.

2) *Azoöspermia* was encountered in all twelve cases in which the seminal fluid was

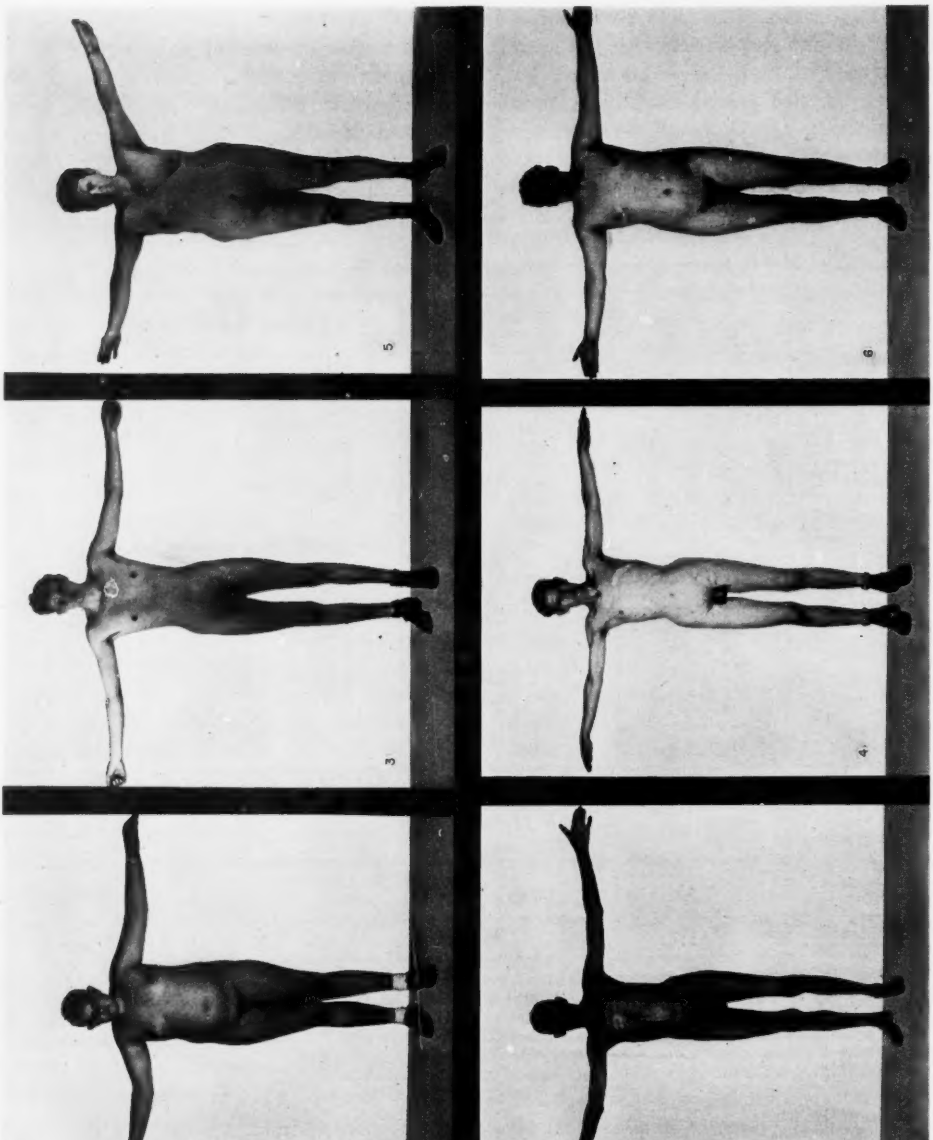

FIG. 1, *Case 2.*
FIG. 2, *Case 3.*

FIG. 3, *Case 12.*
FIG. 4, *Case 11.*

FIG. 5, *Case 18.*
FIG. 6, *Case 20.*

studied. The volume of fluid was often only 0.5 cc. in amount, but in one case was as much as 3 cc.

3) *Gonadotrophic hormone* was excreted in markedly increased quantities in each of the twenty cases. All of the urinary extracts produced vaginal canalization and a 300 to 400 per cent increase in uterine weight over that of control rats. Such canalization and uterine-weight increase were encountered in only one-fourth of the assays of extracts derived from urines of normal men. The average ovarian weight in the assay rats, following injections of seventy-four separate urine extracts from the twenty patients under discussion, was 80.7 mg. (see table 2). This can be contrasted with an average of 11.3 mg. for 73 separate assays performed upon urines from normal men, which corresponds to the average ovarian weight of uninjected control rats.

Luteinization of follicles and formation of discrete corpora lutea were occasionally noted in the ovaries of rats receiving extracts of urines from the patients. This, together with the finding of thick, non-translucent, non-ballooned uteri in the same animals, also suggests progestational activity. The two findings together indicate that both follicle-stimulating hormone and interstitial-cell-stimulating hormone (luteinizing hormone) were being excreted in the urine. Extracts from *Cases 10* and *19* were injected into hypophysectomized rats with resultant stimulation of the ovaries to 55 and 56 mg., respectively. No evidence of luteinization was noted.

The variable features will be discussed as they relate to the three clinical subdivisions of prepuberal hyalinization of the seminiferous tubules. There is no clear demarcation between the three subdivisions since all stages between the completely normal and the completely eunuchoidal habitus were encountered. Therefore an arbitrary classification was made. Each patient was scored for each observation and the total score was used to determine the group in which the patient belonged. Case numbers in tables 1 and 2 run serially from *Case 1*, who had the lowest score, to *Case 20*, who had the highest score.

I. *The eunuchoidal group* (*Cases 1* through *5* and illustrated by figures 1 and 2) ranged in age from 18 to 55 years.

Skeleton. Stature was neither remarkably tall nor unusually short. The span was significantly greater than the height in three cases. The lower measurement was significantly greater than the upper measurement in each case. This finding illustrates that each had eunuchoidal skeletal structure and can be used to date the occurrence of partial or complete failure of Leydig-cell function to the prepuberal period. Delay in osseous development occurred in only one instance (*Case 4*).

Gynecomastia was not a prominent feature in this group. Two cases had none. *Case 2*, who was obese, had fatty breasts, but no palpable breast tissue was distinguishable and nipples and areolae were not enlarged. *Case 5* had questionable breast enlargement, and in *Case 4* the enlargement was slight but definite and had existed since puberty. *Cases 1*, *2* and *5* had microscopic changes in the breast which showed growth greater than that usually encountered in normal male breasts. *Cases 3* and *4* showed normal mammary tissue.

The external genitalia were infantile in *Cases 1* and *2* and moderately delayed in development in *Cases 3* and *5*. Genitalia in *Case 4* were considered normal. Erections occurred at will in all cases, but ejaculations were claimed to be absent in four cases and in the fifth occurred so infrequently that seminal fluid collections were not obtainable. *Case 3* claimed to have had satisfactory ejaculations for forty years, but stated that failure had occurred in the past six months. *Case 4* claimed ejaculations occurred for several years after the onset of puberty, but that he had not experienced them during the past ten years.

The pitch of voice was high in *Cases 1* and *2*, "cracked" occasionally in *Case 4*, and was normal in the other two.

Hair distribution showed delayed development in each of the five cases, as can be seen in table 1.

Muscular development and strength were very poor in *Cases 1* and *3* and were moderately poor in the other three patients.

The Leydig cells presented a generally poor condition in these patients (see following paper).

17-ketosteroid values were lower than in the other two groups.

FIG. 1, *Case 2*.
FIG. 2, *Case 3*.
FIG. 3, *Case 12*.
FIG. 4, *Case 11*.
FIG. 5, *Case 18*.
FIG. 6, *Case 20*.

Estrogen excretion was low in the four instances tested.

II. *The moderately eunuchoidal group* (*Cases 6* through *16* and illustrated by figures 3 and 4) ranged in age from 18 to 69 years.

Skeleton. Stature was more often tall than short. Six of the eleven subjects in the group were at least six feet tall, but short individuals were included. Span was greater than height in only 5 instances, but the lower measurement was significantly greater than the upper measurement in all cases. Thus each patient had some of the stigmata of the eunuchoidal habitus, indicating that partial failure of Leydig-cell function had occurred prepuberally. Appreciable delay in osseous development was not discovered in any of the eight cases in which studies of the bone age were made.

Gynecomastia occurred in six of the eleven cases, but was minimal in four, moderate in one, and marked in the remaining patient. Thus gynecomastia does not always accompany the syndrome in individuals classed as eunuchoidal or moderately eunuchoidal. Deviations from the picture usually encountered in the normal male were seen in six of the eight cases in which breast biopsies were studied. In *Cases 9* and *10* the biopsies showed normal male mammary tissue.

Hair distribution was inconstant in that recession of scalp hair varied from none to complete baldness. Facial hair was absent in six, sparse in four, and normal in one. Axillary hair was always present but was sparse in two. The pubic escutcheon varied from female to normal male in type. None of the subjects had body hair. Extremity hair varied in amount from normal to absent.

Muscular strength and development was judged to be within lower limits of the normal range in nine cases and to be poor in *Cases 6* and *14*.

The Leydig cells presented a somewhat better appearance than in the eunuchoidal group.

Excretion of 17-ketosteroids was judged to be below the limits of normal variation in six of the ten cases assayed and to be below the average normal but within normal range in three additional cases. *Case 14* was slightly above the average normal.

Estrogen excretion was low in five cases and within normal limits in three others. In none was estrogen excretion elevated.

III. *The normal group* (*Cases 17* through *20* and illustrated by figures 5 and 6) ranged in age from eighteen to thirty-two years. Some of these subjects had a few features in common with the other two groups, but all approached normality.

Skeleton. Stature was tall in *Case 18*, short in *Case 19*, and average in the other two. Span was not significantly greater than height in any instance. The lower measurements were greater than the upper measurements in two instances and equal in the other two. None had delayed osseous development. From the skeletal measurements it must be concluded that slight retardation of maturation occurred in two cases and none in the other two.

Gynecomastia was striking in all four cases and in each instance deviations from the normal microscopic appearance of the breasts were seen.

External genitalia were considered normal in each instance. In *Case 17* the hypospadias contributed to the small size of the penis, which was, however, normal in circumference.

Pitch of voice was normal in all four.

Hair distribution. Each of the four subjects had normal hair development of the axillae and extremities and exhibited normal recession of scalp hair. Facial hair was absent in *Case 17*, sparse in *Cases 18* and *19*, and abundant in *Case 20*. *Cases 17* and *20* had normal male escutcheons whereas *Cases 18* and *19* tended toward the female type. Only *Case 20* had body hair.

Muscular strength and development were judged to be normal in each case.

Leydig cells were numerous in this group and their appearance, in general, was approximately normal.

Excretion of 17-ketosteroids was within normal limits in all cases, but fell slightly below the average for normal in three subjects and was at the lower limits of normal in *Case 17*.

Estrogens were not elevated in any instance, but were judged to be within normal limits for three cases and lower than normal in one.

Symptoms of the male climacteric were prominent clinical features in *Cases 3*, *9* and *14* and symptoms suggestive of the climacteric were

observed in several additional cases. The symptoms noted by the former three patients included hot flashes, headaches, pruritis, parasthesias, muscular aches and pain, weakness of muscles of the lower extremities, nervousness, irritability, worrying, depression, and loss of potentia. These symptoms disappeared during substitution therapy, lending credence to the idea that they were of climacteric origin. The 17-ketosteroids were low in *Cases 3* and *9* and entirely normal in *Case 14*.

Cases 1, *4*, *6*, and *20* complained of nervousness, irritability, worrying, depression, and had anti-social tendencies. These symptoms were abolished with substitution therapy. The similarity of the symptoms to those of the climacteric and the response to therapy in these four cases suggests that they may be early manifestations of the climacteric. It is interesting that this group of seven cases with climacteric symptoms included all of the cases over the age of twenty-five years.

Miscellaneous studies included complete physical examination and routine urinalysis and complete blood counts which were within limits of normal variation in all patients. Blood cholesterol determinations, likewise, did not deviate from normal. In the occasional case tested, the fasting blood-sugar level was normal. Basal metabolism determinations, performed on the majority of cases, showed no consistent deviation from the average. The three Negro patients, *Cases 3*, *9* and *14*, had positive serological evidence of syphilis. In addition *Case 9* had hypertensive heart disease, and *Case 14* had paresis (treated successfully with malarial inoculation). *Case 18* exhibited multiple dense fibrosing lesions in many bones and hyperostosis frontalis interna.

Skull roentgenograms. In the sixteen cases in which lateral views of the skull were taken, no abnormalities of the sella turcica were seen. Frontal-sinus development was normal except in *Case 14*, in whom complete absence was noted bilaterally, and in *Case 17*, who had absence on the right and a small sinus on the left.

DISCUSSION

Constitution of the syndrome. In their original description of the syndrome involving hyalinization of the seminiferous tubules, azoöspermia and elevated gonadotrophins, Klinefelter, Reifenstein and Albright (3) included only cases having gynecomastia. We have demonstrated that the syndrome may occur without the association of demonstrable gynecomastia. This is demonstrated by seven patients in the eunuchoidal and moderately eunuchoidal groups. Because they lack gynecomastia, these cases cannot be regarded as examples of the syndrome, as originally described; yet we hesitate to call these cases examples of a new and separate clinical syndrome.

Klinefelter, Reifenstein and Albright (3) also indicate that the syndrome should include only patients "without A-leydigism" or with "isoleydigism." Their schematic drawings show a lesion involving only one of the two testicular functions, namely, the production of spermatozoa. From their clinical description and 17-ketosteroid determinations we conclude that their own *Case 5* must have had at least partial failure of the second testicular function, namely, the production of hormone. We agree that the lesion in this syndrome always involves the gametogenic function of the testis and, in addition, may involve the endocrine function to a greater or lesser degree. We, likewise, hesitate to designate our cases with Leydig-cell failure and associated eunuchoidism as examples of another new and separate syndrome.

Since the gynecomastia advances by imperceptible stages from complete absence through slight and moderate to marked hypertrophy in different individuals and since the maturation is staggered in various stages from eunuchoidal to mature normal, we prefer to enlarge the original syndrome so that it may include those subjects who have little or no gynecomastia and also those who have partial failure of Leydig-cell function. In order to include these individuals, we have used the device of requiring the patient to have certain constant features necessary for admission to the syndrome. He is then placed in one of the three subdivisions according to the number and degree of the variable features he exhibits.

Explanations of the elevation in gonadotrophins. No correlations could be established between the amount of gonadotrophin excre-

tion and the histological appearance of the Leydig cells, the clinical status of the patient or the 17-ketosteroid excretion. This finding may be partially accounted for by the fact that sufficiently large amounts of hormone were present in the extracts of the overnight specimens so that ovarian-weight responses occurred at the maximal or insensitive level of the dosage-response curve. Thus moderate differences in gonadotrophin excretion would not be detected. The procedure, however, offered the advantage of detecting augmentation of the increased output of follicle-stimulating hormone by any interstitial-cell-stimulating hormone present in the urine. This was manifested by the occurrence of luteinization of the ovaries and progestational changes in the uteri. It may be unfair to say that the detection of interstitial-cell-stimulating hormone represents increased excretion of that factor. It would perhaps be more reasonable to interpret this finding as indicating that enough follicle-stimulating hormone was being excreted for augmentation to be detectable with normal amounts of interstitial-cell-stimulating hormone. The few experiments with hypophysectomized rats tend to bear this out.

Klinefelter, Reifenstein and Albright (3) suggest that the elevation of gonadotrophins is secondary to the lack of production of "inhibin" by the hyalinized seminiferous tubules. At least two considerations militate against this: 1) lack of proof for the existence of "inhibin"; 2) lack of proof that the seminiferous tubules normally produce "inhibin" or any other hormone.

One explanation for these observations is that the anterior pituitary is sufficiently sensitive to deflections in circulating steroid levels that it responds by increased secretion of gonadotrophins as soon as the steroid level is depressed even slightly below normal. This view takes cognizance of the fact that different end-organs have different thresholds of sensitivity for the steroids. It is postulated that the anterior pituitary is more sensitive than other end-organs to slight decreases in blood androgens. Such minor decreases would be too slight to be reflected in other end-organs. *Patients 17* through *20* illustrate this well in that gonadotrophins are high, the secondary sex characteristics remain normal, and 17-ketosteroids are within the lower limits of normal variation and may well be lowered for the individuals involved. Animal experimentation by Nelson (10) has shown that the pituitaries of rats made cryptorchid by operation show castration-cell changes months before the Leydig-cell failure is sufficient to cause decreases in prostate weight and seminal-vesicle weight. The seminiferous tubules undergo atrophy long before the Leydig-cell failure occurs. The interpretation offered is that only partial Leydig-cell failure occurs early, and that the pituitary responds to the early shift in steroid level while the seminal vesicles and prostate glands, having lower thresholds, continue to be stimulated by the lower level of Leydig-cell secretion.

A second explanation is that the rise in gonadotrophins is a direct consequence of the failure of the seminiferous tubules to utilize F.S.H. Such an explanation would reconcile the concomitant occurrence of high gonadotrophin and normal 17-ketosteroid levels in the same individual, since the function of the Leydig cell need not be drawn into the discussion. It would not necessitate postulating the existence of a "second hormone" of the testis. The explanation is based upon the hypothesis that the seminiferous tubules metabolize and inactivate the follicle-stimulating hormone of the anterior pituitary, which is the specific stimulator of the tubules. Thus tubular failure would interfere with tubular inactivation of the follicle-stimulating hormone and consequently rises in blood levels and increases in urinary excretion and hypophysial content of this hormone would occur.

The same explanation can be applied to the early castration-cell changes in the pituitaries of cryptorchid rats (10). Both castrational cells and atrophy of the tubules occur months before histological or functional evidence of Leydig-cell failure takes place. It could be reasoned that rises in follicle-stimulating hormone result from lack of inactivation by the failing seminiferous tubules and that when hypophysial potency rises it is accompanied by cellular changes recognized as "castration cells." A summary of the hypothesis as it applies to the ovarian hypophysial relationship

can be found in an earlier communication (11). More recent experiments designed to test the hypothesis in female rats indicate that rat ovaries metabolize gonadotrophins (12).

Correlation of the 17-ketosteroid excretion with the clinical picture. Clinically each patient exhibited some deviation from normal that could be attributed to the presence of less than the normal amounts of circulating androgen. In *Case 19* this was manifested only by the lack of beard and in *Case 20* only by very mild climacteric symptoms. However, all the other cases had more marked signs of eunuchoidism or androgen deficiency. This seems to be reflected in the 17-ketosteroid excretion, which averaged 4.04 mg. per 12 hours for the 19 patients tested as contrasted with an average value of 6.89 mg. for normal men. Although the 17-ketosteroid excretion of 11 subjects fell within the lower limits of normal and 6 others were distinctly below normal, it is noteworthy that only 2 subjects had values above the average normal (*Cases 2* and *14*). These two subjects, however, exhibited clinical features of marked androgen lack. The explanation for this dichotomy may be drawn from the excellent chromatographic studies of urinary steroids made by Dobriner (13). He showed that among the many steroids that comprise the complex of 17-ketosteroids, two existed in greater amounts then the others, namely, androsterone (which is active androgenically) and 3-α-OH-aetiocholanone (which is inactive androgenically). In pregnancy, senility, certain cancers and adrenal tumors the androgenic steroids may be reduced and the inactive steroids elevated. The normal 17-ketosteroid values encountered in these two cases, which show androgen lack clinically and poor Leydig cells microscopially, may be due to the preponderant excretion of such biologically inactive steroids as aetiocholanone.

In other subjects a good correlation exists between the clinical picture and the amount of 17-ketosteroids excreted. For example, *Cases 15* through *20* represent the subjects with fewest clinical signs of androgenic failure and all excrete amounts within the range of normal. Among the remaining cases showing greater clinical evidences of androgenic failure, 6 instances are encountered with excretion values below the lower limits of normal, several more just on the borderline, and only one above 4 mg. (in addition to *Cases 14* and *2, vide supra*).

Time of onset of the syndrome appears to be at or before puberty. This can safely be stated for all cases with abnormal skeletal proportions and some lack of development of the secondary sex characteristics. In the cases with little or no deviation from normal in these respects (*Cases 17* through *20*), the syndrome cannot definitely be dated to puberty. However, the onset of the gynecomastia occurred at that time and this fact suggests a possible time relationship.

Further failure of Leydig-cell function associated with symptoms of the male climacteric seems to occur with increasing age in these patients. All of the subjects over age 25 had some symptoms of the male climacteric and 3 subjects had the full-blown syndrome (14). We interpret the finding of climacteric symptoms in this syndrome as meaning that: 1) the Leydig-cell function must have been partially present for a long time; and 2) further failure occurred, thus accounting for the withdrawal symptoms. Climacteric symptoms are not seen in other types of eunuchoidism in which no antecedent Leydig-cell function has occurred. Thus the Leydig cells in these patients have an abnormal distribution and an abnormal appearance; they function poorly; and they fail early.

SUMMARY

A study of the clinical characteristics, hormonal excretion and testicular biopsies of 20 patients with hyalinization of the seminiferous tubules has led us to expand the limits of the syndrome recently described by Klinefelter, Reifenstein and Albright. In order to be admitted to the present category, a patient must have the following: A) *Constant features* which are invariably present—1) small atrophic testes in which biopsy reveals hyalinization of the tubules and clumping of Leydig cells, 2) azoöspermia, 3) elevation of urinary gonadotrophins. B) On the basis of their *variable features* the patients are further classified as belonging to one of the following 3 subdivisions: 1) eunuchoidal, 2) moderately eunuchoidal, or 3) normal. These variable features include: a)

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skeleton which may or may not exhibit delay in osseous development and may show eunuchoidal or normal measurements; b) gynecomastia which may be marked, mild or absent; c) external genitalia which vary from completely infantile to entirely normal; d) the pattern of hair distribution may be prepuberal, puberal or normal adult in type; e) pitch of voice may be high or low; f) muscle development and strength vary from poor to normal; g) Leydig cells vary in quality; h) 17-ketosteroid excretion may vary from normal to very low; i) estrogens are not elevated, but may be normal or low.

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Hyalinization of the Seminiferous Tubules Associated with Normal or Failing Leydig-Cell Function. Microscopic Picture in the Testis and Associated Changes in the Breast[1,2]

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Significant studies upon testicular degeneration have been recorded by Simmonds (1), Stieve (2), Rossle (3), Sand and Okkels (4), Engle (5), Charny and Merance (6) and Warren and Olshausen (7). These reports have dealt with changes in the interstitial cells of Leydig as well as the seminiferous tubules and some attention has been given to the relation of testicular morphology to the condition and function of the accessory reproductive organs. However, much information is left to be desired as to the relation between testicular morphology and the production of androgenic hormone. In this study an opportunity was presented to survey the structure of testes obtained at biopsy from a group of patients whom we regard as presenting evidence of some degree of failing function of the Leydig cells. Inasmuch as the survey of these patients (Heller and Nelson, 8) has included a wide variety of clinical and hormonal studies the opportunity to compare structure and function was provided. In addition, we have studied the microscopic anatomy of the breasts of these patients since many of the latter presented a picture of gross gynecomastia.

PROCEDURES

Biopsies from testes and breasts in each case were fixed in Bouin's fluid and in neutral formol. The usual size of the testicular biopsies was 4×4×5 mm. although smaller pieces were taken from the more atrophic testes. Testicular material fixed in Bouin's fluid was sectioned at 5 micra and representative sections were stained with hematoxylin and eosin, Masson's stain, iron hemotoxylin and erythrosin, and orcein (for elastic fibers). Formol-fixed material was sectioned with the freezing microtome and subjected to the following procedures: post-osmication, Sudan III, Schultz reaction (for cholesterol), and study with the polarizing microscope. Mammary tissue was sectioned serially at 8 micra, every tenth section was mounted, and alternate slides were stained with hemotoxylin and eosin and Masson's stain.

The testes of the 19 patients included in this study were uniformly small, varying in size from that of a pea to that of an almond. The microscopic picture always showed atrophic changes in the germinal epithelium, sclerosis

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TABLE 1. SUMMARY OF OBSERVATIONS ON TESTICULAR BIOPSIES FROM PATIENTS *1–20*

	Case No.	Sclerosis of Tubules	Fibrocytes	Leydig Cells								17-Ketosteroids mg./12 hrs.
				Number	Pigment Granules	Crystalloids	Birefringency	Schultz Reaction	Sudan	Granules	Function	
Eunuchoidal	*1*	4	3	2–3	0	0	3–4	3	2	1–2	1	3.45
	2	2–3	3	1	0	0	3–4	3–4	3	0–1	1	6.9
	3	3	3	2	3	0	2–3	1–2	2	0–1	1	3.9
	4	3–4	3	1–2	2–3	0	1	0	1	1	1	0.6
	5	1–2	3	1	0	0	0	0	1	1	1	2.9
Moderately Eunuchoidal	*6*	1–2	2	1	0	0	1–2	0	1	0–1	1	2.5
	8	3–4	3	1	0	0	0–1	0	1	0–1	1	—
	9	3	2	2	3	0	0	0	1	0–1	1	2.0
	10	2	3	2–3	1	0	1–2	0	2	2	2	2.7
	11	3	3	3	0	0	1–2	0	3	2–3	4	3.5
	12	4	3	1–2	1	0	0–1	0	1	1	1	2.9
	13	3	1–2	2–3	0	0	0–1	0	1	2	2	3.3
	14	3	1–2	3–4	2	0	2	1	2	2–3	4	6.9
	15	3	3	2	0	0	1	0	1	1	2	4.1
	16	3	3	4	0	0	2	0	3	2–3	3	4.9
Normal	*17*	3–4	2	2	0	3	2	1	2	2	2	3.4
	18	3	3	4	0	0	3	2	2	1	3	6.4
	19	3	2	4	0	1	2–3	2	3	2–3	3	5.0
	20	2	2	3	0	1	3–4	3–4	2	3	4	4.0

Ratings for column on Function: 1 = Poor; 2 = Fair but Failing; 3 = Good but Failing, 4 = Good.
Other ratings explained in text.
Only Sertoli cells were found in such tubules as were not completely sclerosed with the exception of *Cases 2, 5* and *6*. *Case* 2 showed two tubules with all stages of spermatogenesis, *Case 5* showed primary spermatocytes and spermatogonia in a few tubules and *Case 6* showed tubules with various stages ranging from spermatogonia to spermatozoa.

of the tubular lamina propria and an unusual degree of clumping of the interstitial cells of Leydig. The testes showed variations in the degree of these changes and in the cytological condition of the Leydig cells. Table 1 presents in summary form the observations on each of the biopsies. It will be noted that many of the columns show observations rated on a 0 to plus 4 basis. An explanation of these ratings is important and will be given in the following paragraphs.

The sclerotic process in the seminiferous tubules (see figs. 2 and 3) which is characteristically seen in these testes involves the basement membrane and the tunica propria of the tubules. In the normal testes the basement membrane is a very thin delicate structure and is surrounded by a few collagenous and elastic fibers. All of the testes in this group of patients show widespread thickening of these elements. The elastic fibers usually seem to be decreased in number and always are crowded toward the periphery while the collagenous fibers appear to be increased in number and size. Coincident with progression of the fibrosis a deposition of hyaline material occurs and the end result of

EXPLANATION OF FIGURES

FIG. 1. (Top left). Biopsy of normal testis. Biopsy no. 114. Spermatogenesis in progress and interstitial cells in good functional condition. ×125.

FIG. 2. (Top right). *Case 6*. Testicular biopsy. Sclerosis of tubules. One tubule essentially normal and shows all stages of spermatogenesis. Two tubules show early sclerotic changes with spermatogenesis in progress but diminishing. Two tubules with early sclerosis and two with advanced sclerosis show spermatogonia and Sertoli cells only. Interstitial cells scanty in number and in poor functional condition. ×125.

FIG. 3. (Middle left). *Case 6*. Testicular biopsy. This is a field from the same section as fig. 2 and shows advanced stages of sclerosis. Seven tubules with Sertoli cells only. Many tubules completely or nearly completely sclerosed and hyalinized. ×125.

FIG. 4. (Middle right). Biopsy of normal testis. Biopsy no. 114. Nest of interstitial cells in good functional condition. Note particularly the aggregated perinuclear granules. ×450.

FIG. 5. (Bottom left). *Case 20*. Testicular biopsy. Small clump of interstitial cells in good functional condition. Moderate number of fibrocytes present. Two sclerotic tubules. ×450.

FIG. 6. (Bottom right). *Case 1*. Testicular biopsy. Clump of interstitial cells in fair functional condition. Many fibrocytes and fat cells. Two sclerotic tubules. ×450.

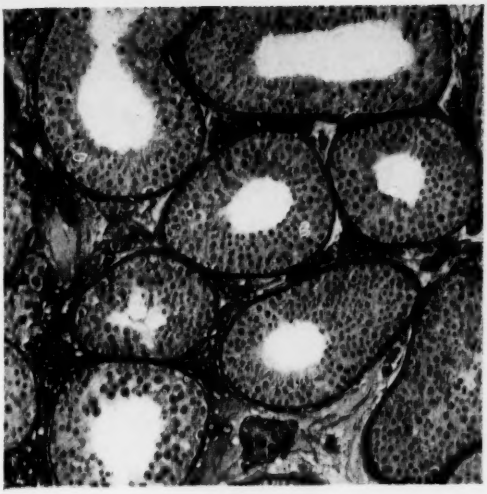


Figure 1

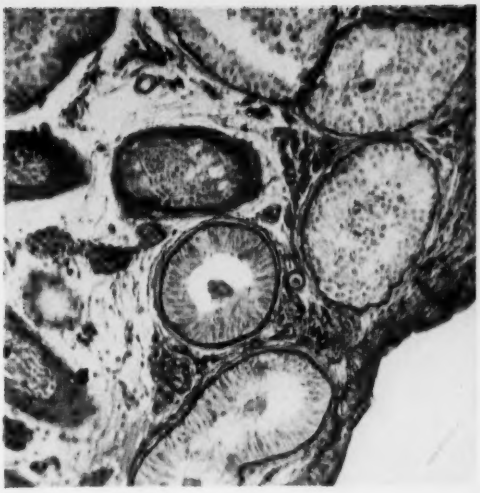


Figure 2

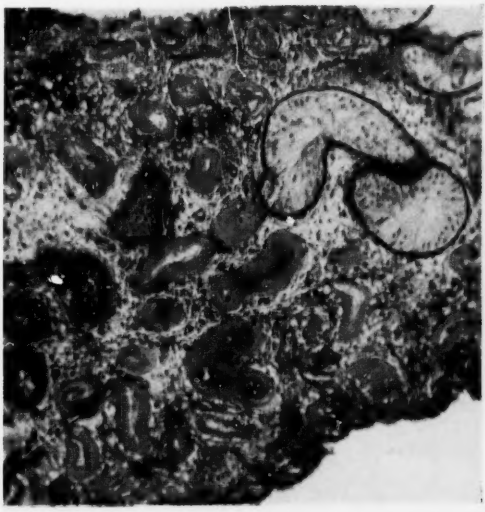


Figure 3

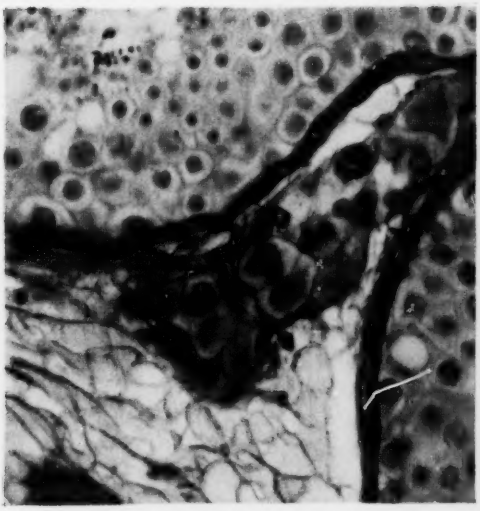


Figure 4

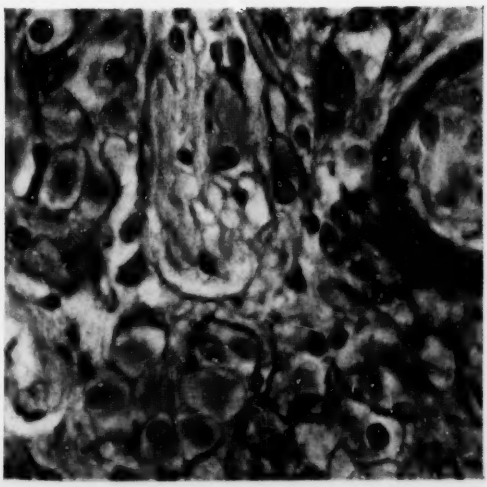


Figure 5

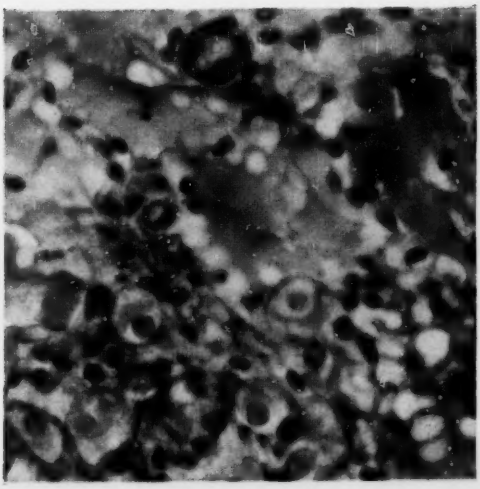


Figure 6

this process is complete sclerosis of the tubule giving the latter the appearance of a small irregular hyaline structure. With extension of the fibrotic process the germinal elements show progressive involution. Most of the tubules contain Sertoli cells only or are completely hyalinized. A rating of 1 to 2 on our scale indicates early stages of thickening in the basement membrane and tunica propria; 3 indicates widespread, advanced sclerosis; and 4, complete or nearly complete hyalinization of all tubules.

The Leydig cells were studied in detail both as to number and as to cytological characteristics. A brief consideration of the latter, based principally upon our observations on normal testes, is important for an understanding of the relations which will be described.

The cells normally are found singly or in small compact groups (fig. 4). They are usually ovoid or polyhedral and in our material vary in size from 14 to 25 micra in diameter. The nuclei are large, vesicular, usually eccentric and contain one or two large, peripherally placed nucleoli. The chromatin material is present in diffuse granular masses which usually are located around the periphery of the nucleus. The most conspicuous elements of the cytoplasm are the crystalloids and pigment granules. The former show a variety of sizes and shapes, in some instances being smaller than the nucleus and in others being almost as long as the cell. They are usually rod-shaped, but may be round or ovoid and they may occur anywhere within the cell. By no means do all cells contain crystalloids and their significance is uncertain. The pigment granules are regarded as being composed of lipofuscin, a waste pigment. They present a variety of sizes, lack a constant distribution, and may clump. They are rarely seen in the testes of vigorous, young subjects and they increase with age. Of considerably greater significance are the refractile granules, which we believe are closely related to the functional activity of the Leydig cell. The granules, for the most part lipoidal in nature, present two principal patterns of form and distribution: (1) coarse, irregularly dispersed granules which may be found anywhere in the cell, and (2) small granules aggregated in the perinuclear area. The latter may be so dense as to present the appearance of a homogeneous mass. The region they occupy encompasses the attraction sphere and Golgi apparatus and in some instances may be so extensive as to fill most of the cytoplasmic area. Some cells show both types of granules while others contain one type only. Vacuoles are seen occasionally in various regions of the cell and appear to be related to degenerative processes since they are encountered most frequently in cells which seem to be undergoing atrophy. It should be noted that in the bull Hooker (9) reports that vacuolation of the interstitial cells appears to be related to their maximum function.

The number of Leydig cells for each patient was estimated by examining at least 50 sections from each biopsy. A rating of 1 was given to those testes which showed about the average number of Leydig cells that are seen in a comparable volume of a normal testis. The ratings 2, 3 and 4 indicate progressive increases over the numbers of cells seen in comparable volumes of normal testes. In the estimates all cells which were judged to be Leydig cells whether they were in good functional condition or not are included. It should be noted that we have not attempted to make actual counts of Leydig cells and we realize that this type of estimate is subject to error. However, it does provide a basis for comparison since the intertubular areas in the testes of all patients were approximately equal. It is important to note that the rating of these testes in terms of the normal testis has been arbitrarily selected as a basis of comparison only. The wide-spread decrease in the volume occupied by seminiferous tubules produces the picture of an apparent increase in intertubular cells. Thus the total number of Leydig cells in a testis given a 3 or 4 rating might not have been greater, and probably was less, than in a normal testis. It is also recognized that, of necessity, our biopsies have been samples only and the average picture for any given testis may not be represented.

In the rating of fibrocytes a similar basis was used. A rating of 1 indicates about the same number as is seen in the normal testis while the successively higher ratings represent increasingly greater numbers of fibrocytes.

Pigment granules in the Leydig cells were rated from 0, indicating no granules, and 1 in-

dicating a small number of cells with a few granules, to 3 in instances in which cells with granules were numerous. In no case were pigment granules as numerous as in testes from very old men.

The number of crystalloids in the Leydig cells was rated on a similar basis.

The presence of birefringent material in the Leydig cells, as shown in unstained frozen sections studied with the polarizing microscope, was rated as 0 in instances in which no optically active material could be seen, 1 when small scattered areas were present, 2 or 3 in testes with larger areas of birefringency and 4 in cases in which optical activity was general throughout the specimen.

The Schultz reaction for cholesterol was rated on the basis of the extent and intensity of the green coloration in the intertubular areas

The Sudan preparations were judged in a similar fashion, only the deposits of stain in the Leydig cells being considered in the rating. According to Lison (10) all lipids show deposits of stain in Sudan preparations. Birefringency is not a characteristic of glycerides and fatty acids in the liquid state, but they may become crystalline and birefringent upon cooling. However, they never show the cross of polarization which may be found in the presence of cholesterides or lipins. Since our observations on the presence or absence of the cross of polarization have shown no consistency we have made no distinction in the nature of birefringency in the table. Lison states that the absence of birefringency does not rule out the presence of any lipid since under some circumstances cholesterides and lipins may not show birefringent characteristics. The Schultz reaction (derived from the Liebermann-Burchardt reaction) when positive proves the presence of cholesterol or its esters but, according to Lison, a negative reaction does not definitely prove their absence. In the table no reference is made to the osmicated preparations since they paralleled closely the observations on Sudan preparations.

The presence and extent of granules in the Leydig cells were rated from 0, indicating the absence of granules, to 3 in testes with moderately heavy granulation. No distinction is made in this rating between the two types of granules.

OBSERVATIONS ON TESTICULAR BIOPSIES

EUNUCHOIDAL GROUP

Patients 1–5, who are included in the eunuchoidal group, presented a variety of testicular changes. Although the seminiferous tubules of these patients were uniformly small and atrophic, and usually contained Sertoli cells only, two of them, Nos. 2 and 5, showed cells of the germinal line. The biopsy from *Case 2* contained two tubules which presented all stages of spermatogensis although this process appeared to be proceeding at a greatly retarded rate. *Case 5* showed a few tubules with primary spermatocytes. The sclerotic process varied from 2 to 4 in this group.

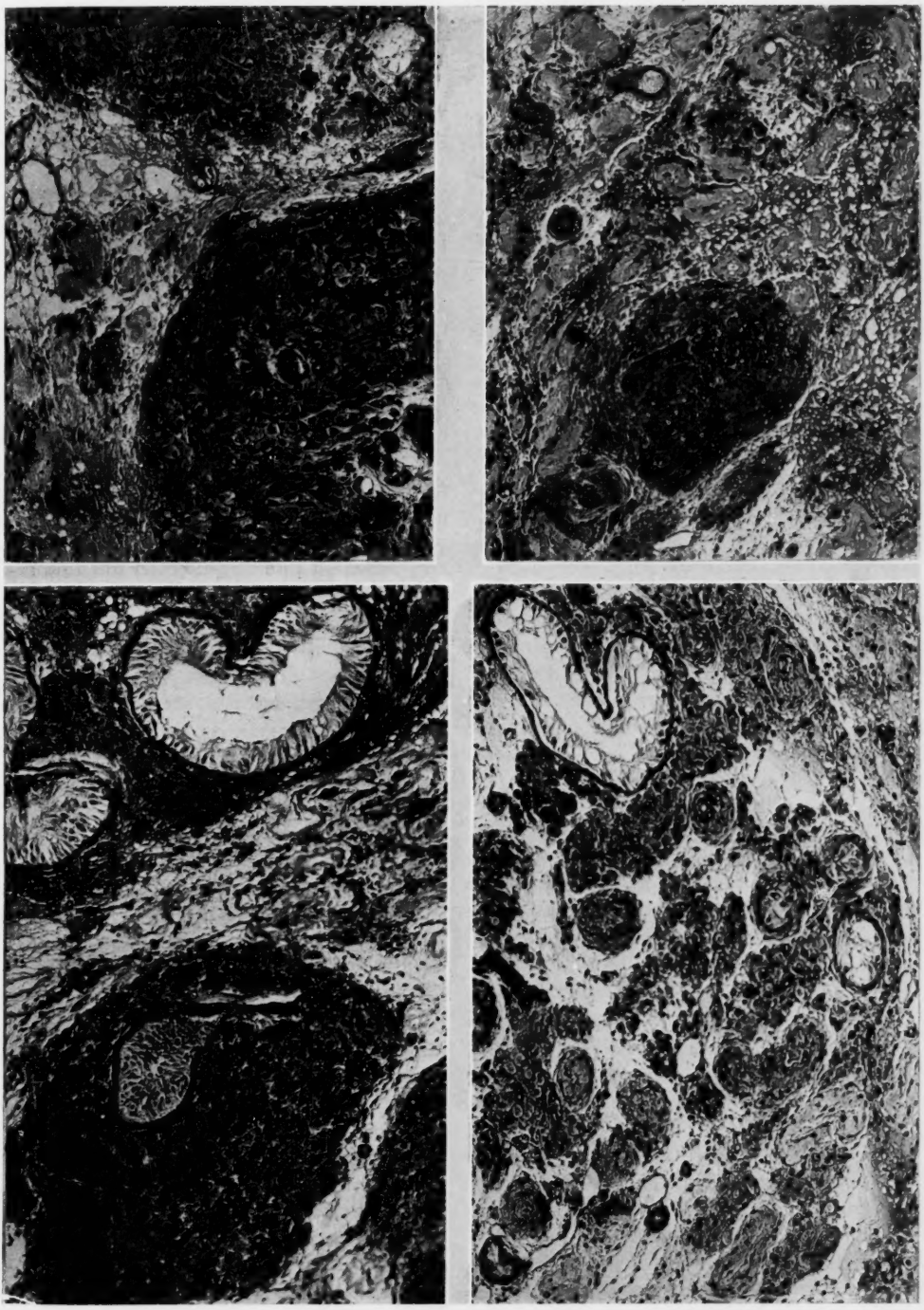
Interstitial cells of Leydig were rated from 1 to 3 in number and in each instance, with the exception of *Case 3*, they were present in small nests or small clumps. *Case 3* showed medium-large clumps of cells. Fibrocytes and fat cells were numerous in this group and the impression was distinct that transformations between Leydig cells and fibrocytes (fig. 6) were in progress and that the Leydig cell population was decreasing. Pigment granules were absent or scarce except in *Case 3* in which a rating of 3 can be explained on the basis of the patient's age, 55 years.

FIG. 7. (Top left). *Case 11.* Testicular biopsy. Two large clumps of interstitial cells. Most cells in good functional state although some show degenerative changes. Fibrocytes and fat cells present, but not numerous. ×125.

FIG. 8. (Top right). *Case 12.* Testicular biopsy. One medium-sized and several small clumps of interstitial cells. Most cells in poor functional condition and many are undergoing degenerative and transitional changes. Fibrocytes and fat cells very numerous. Many small, completely hyalinized tubules. ×125.

FIG. 9. (Bottom left). *Case 16.* Testicular biopsy. Two large and one small clump of interstitial cells. Many cells in good functional condition, but degenerative and transitional changes are common. Three tubules showing early sclerosis and containing Sertoli cells only. ×125.

FIG. 10. (Bottom right). *Case 20.* Testicular biopsy. Numerous small clumps of interstitial cells. Most of cells are in good functional condition, but degenerative changes are evident and fibrocytes are fairly numerous. Many completely hyalinized tubules and one tubule with Sertoli cells only. ×125.



FIGS. 7–10. See opposite page for description.

Crystalloids were absent uniformly in the Leydig cells of these biopsies and binucleated cells were seen only rarely.

Ratings for birefringency and the Schultz reaction presented considerable variation within this group but the two preparations showed good agreement for individual cases. Granules were scarce in all except *Case 1* (fig. 6) in which they approximated the condition of the normal testis. The impression was distinct that the Leydig cells had either been in a poor functional state for some time or, in other instances, that they were undergoing functional failure at the time of biopsy.

MODERATELY EUNUCHOIDAL GROUP

With the exception of *Case 6*, whose testis showed a few tubules with all stages of spermatogenesis (fig. 2), all the patients in this group had testes whose tubules were very small and were either completely sclerosed or showed Sertoli cells only (figs. 8 and 9).

Leydig cells varied in number from 1 to 4 in these patients, most cases being rated at 2 or 3. The cells usually occurred in clumps varying in size from small to large (figs. 7, 8 and 9). The clumping was much more distinct in these patients than in the eunuchoidal group with the exception of *Case 6* whose cells were grouped in small nests. Fibrocytes were, in general, somewhat less numerous than in the eunuchoidal group but again the impression was distinct that the cells were in a state of failure. Stages of transformation between Leydig cells and fibrocytes or fat cells were evident in each instance (figs. 8 and 9) although less marked in *Cases 11* and *14* (fig. 7). Pigment granules were conspicuous only in *Cases 9* and *14*, ages 69 and 27, respectively. Although none of the testes showed Leydig cells with crystalloids, in almost every instance binucleated cells were encountered fairly frequently.

Birefringent material was somewhat less conspicuous in this group than in the eunuchoidal group, only *Cases 14* and *16* receiving a full rating of 2 on this point. Only one case, *No. 14*, showed a positive Schultz reaction. However, granules were encountered more commonly in the Leydig cells and approximated the normal condition in *Cases 11*, *14* and *16*.

Normal group. In all of the four patients included in this group the testes showed a picture of very marked tubular sclerosis. Sertoli cells were encountered only in such tubules as were not completely hyalinized (figs. 5 and 10).

Leydig cells were more numerous in this group than in the others and most of them were arranged in medium-sized to large clumps. Fibrocytes were numerous and, with the exception of *Case 20* (fig. 5), the evidence was distinct that Leydig cell-fibrocyte transformations were in progress. Pigment granules were not encountered in this group, but three of the cases, *Nos. 17*, *19*, and *20* showed Leydig cells with crystalloids. In all instances binucleated cells were present.

Birefringent material was seen in some abundance in all cases and the Schultz reaction was positive in each instance. The Leydig cells were well granulated in this group and in general presented a picture of better function than in the other groups. However, in all instances, except *Case 20*, we believe the morphological picture indicates failing function of the cells.

Normal men. The observations on testicular material obtained at castration or biopsy from eleven men, varying in age from 19 to 65 years, whose hormonal assays and clinical conditions were within the limits of normal variation are included in table 2.

These testes are regarded as normal adult organs according to our standards. The latter include the following criteria: (1) Evidence of active spermatogenesis in at least 80 per cent of the tubules with mature sperm in the majority of these and little or no sloughing of immature cells (figs. 1 and 4). Our observations seem to indicate that it is an exceptional testis that does not contain at least a few atrophic tubules. These, quite reasonably, tend to increase with the age of the individual. (2) Absence of hyaline degeneration of the type described in this paper. This does not take into consideration simple fibrosis which appears to be a normal process in tubular aging and differs somewhat from the hyaline sclerosis observed in our patients. Fibrosis testis, as described by Spangaro, Stieve and Engle involves the basement membrane and tunica propria, but is characterized principally by an

increase in elastic fibers without hyalinization. The result is a gradual decline in tubular size and the assumption of a somewhat woolly appearance. (3) Leydig cells present abundantly in small nests between the tubules. Granulation profuse in most cells. (4) Relative scarcity of fibrocytes and absence or infrequent occurrence of fat cells.

The testes of the eleven men in this group meet the requirements set forth above. In each case active spermatogenesis was in progress although the process showed some retardation and minor degrees of epithelial sloughing were evident in the older subjects. Hyaline sclerosis was absent, but some degree of simple fibrosis was present in the testes of men in the older group. We regard retarded spermatogenesis as related to the occurrence of fibrosis and probably, as stated by Stieve, due to a reduction in the supply of blood to the seminiferous epithelium.

Leydig cells were rated as 1 to 2 in this group and were distributed in a normal pattern. It will be remembered that our arbitrary scale of rating considers 1 as the usual picture in the normal testis. Fibrocytes were present in scattered areas only and fat cells were absent. Pigment granules were present in five of the six men who were at least 58 years old. Crystalloids were present in all instances except *Case 14*. Leydig cells with multiple nuclei were seen in all cases but usually were relatively rare. Birefringent material was present in each testis and the Schultz reaction was positive in all except two. Granules were abundant in this group and the functional appearance of the Leydig cells was regarded as good in each instance (fig. 4).

TABLE 2. SUMMARY OF OBSERVATIONS ON BIOPSIES OBTAINED FROM NORMAL MEN. GOOD SPERMATOGENESIS PRESENT IN ALL CASES. HYALINIZATION ABSENT BUT EARLY FIBROSIS PRESENT IN SOME INSTANCES

Biopsy No.[1]	Age	Fibrosis of Tubules	Fibrocytes	Leydig Cells								17-Ketosteroids mg./12 hrs.
				Number	Pigment Granules	Crystalloids	Birefringency	Schultz Reaction	Sudan	Granules	Function	
8	24	0	1	1	0	1	2	1–2	3	2–3	4	9.12
12	65	1	1–2	1	2–3	1	1–2	1	2	2	3	4.36
26	58	1	1	1	1	3	1	1	2	1–2	3	4.47
31	19	0	1	1	0	1	2	2–3	3	2	4	9.95
40	62	1	1	1–2	2	1–2	1–2	1	2	2	4	13.6
65	58	0–1	1–2	1	2–3	1	1–2	1	2	1	3	—
71	23	0	1–2	1–2	0	3	1–2	1	2	2	4	9.65
75	63	0–1	0–1	1–2	2	2	1	0	2	2	4	—
84	64	1	1–2	1	0	1	0–1	0–1	1	1–2	3	4.8
86	34	0	0–1	2	0	3	3	3–4	3	2	4	—
114	26	0	0–1	2	0–1	0	0–1	0	3	3	4	6.9

[1] Biopsy No. refers to serial number in our series of testicular biopsies.

OBSERVATIONS ON BREAST BIOPSIES

Biopsies were obtained from the breasts of 17 patients. In securing these an infra-areolar incision was made and a liberal piece of tissue was removed from beneath the nipple and areola. Our examination of entire breasts obtained from men at autopsy have indicated that material from this region is most likely to contain representative mammary tissue.

In examining the tissue microscopically attention was given to the number and appearance of ducts, the presence or absence of alveolar structures, and the nature and density of the stroma. Ratings were made for these observations on the basis of 0 to 4 and are recorded in table 3. Comparisons were made with material obtained from biopsies and autopsies on men who showed no evidence of gross gynecomastia and whose endocrine status, both clinically and on the basis of hormonal studies, was normal. In each instance a rating of 0 indicates no departure from the condition regarded as normal for men of the age group in which most of our patients fall (18 to 32 years). Ratings above 0 indicate successively increased amounts of parenchymal structures (ducts and alveoli) and stroma (interlobular and intralobular connective tissue).

The breasts of normal men show a variable

number of ducts, but usually the latter are relatively few in number and the epithelium is low cuboidal (figs. 11 and 12). Alveoli are rarely encountered in our experience. The stroma between the ducts (interlobar and interlobular) is moderately dense collagenous, but occurs only in strands which support the ducts. Elsewhere it is made up of loose collagenous tissue interspersed with fat. Periductal and intralobular connective tissue which is rich in cells and relatively poor in fibers is present in very scanty amounts.

TABLE 3. SUMMARY OF OBSERVATIONS ON BREAST BIOPSIES FROM PATIENTS *1–20*

	Case No.	Gross Rating	Ducts	Alveoli	Interlobular Stroma	Intralobular Stroma
Eunuchoidal	*1*	0	0	1	?	1
	2	4	1	0	3	0
	3	0	0	0	2	0
	4	1	0	0	0	0
	5	1	2	2	1	2
Moderately Eunuchoidal	*6*	1	0	0	2	0
	8	1	2	1	2	1
	9	4	0	1	1	1
	10	0	0	0	0	0
	11	2	0	0	1	0
	12	0	0	0	1	0
	13	0	1	1	1	1
	15	1	0	0	1	0
Normal	*17*	4	4	3	2	2
	18	4	3	3	2	?
	19	4	3	3	3	3
	20	4	2	0	2	1

Eunuchoidal group. Grossly evident increase in breast-size was present in *Case 2* while *Cases 4* and *5* showed a slight increase. The microscopic picture in *Case 2* revealed that the increased size was due to fatty deposits and an increase in the amount of dense interlobular stroma. *Case 5* showed an appreciable increase in the number of ducts, a fair number of alveolar structures and an increase in intralobular stroma (fig. 16). *Cases 1* and *3*, neither of which presented evidence of gross gynecomastia, showed an increase in dense interlobular stroma.

Moderately eunuchoidal group. Some degree of gross gynecomastia was seen in five of the eight patients in this group, but in only two, *Cases 9* and *11*, was the size increased significantly. *Case 9*, rated as 4, showed only slight stromal and parenchymal increases, while *Case 11*, with a rating of 2, showed only a slight augmentation of interlobular stroma. *Case 8*, who was rated as 1 grossly, showed perhaps the most marked microscopic changes while the remaining instances presented minor degrees of hyperplasia (fig. 15). *Case 13*, who manifested no gross gynecomastia, showed an increased amount of parenchymal and stromal tissue.

Normal group. Each of the four patients in this group was accorded a rating of 4 and in each instance the microscopic picture confirmed the gross appearance. Three cases showed alveolar structures and all four had increased numbers of ducts and increased amounts of interlobular and intralobular stroma (figs. 13 and 14).

It is noteworthy that, with the exception of the four patients in the normal group, the gross condition of the breasts did not regularly correspond with the microscopic picture.

The changes seen in the breasts of these patients are not unlike those which were described by Heller, Nelson and Roth (11) in men who were considered to be functional prepuberal castrates. They correspond only partially to the picture that we have observed in the breasts of men who had been treated with stilbesterol. In the latter case the ducts present a condition of hyperplasia and hypertrophy with the ductal epithelium showing a tendency to stratify and to undergo intraductal proliferations. Alveoli are usually, but not always, found in such breasts. Perhaps the most striking change has been the increase in the highly cellular intralobular connective tissue. The interlobular stroma is increased in amount and density but this is somewhat overshadowed by the presence of additional fatty tissue.

The breasts of these patients, even those in which the most marked changes occurred, do not show the same degree of parenchymal growth that we have seen in some instances of puberal gynecomastia (figs. 17 and 18). In the latter, ducts of various sizes frequently are so numerous as to form relatively large lobular structures. Intralobular connective tissue is profuse and interlobular stroma is only moderately dense.

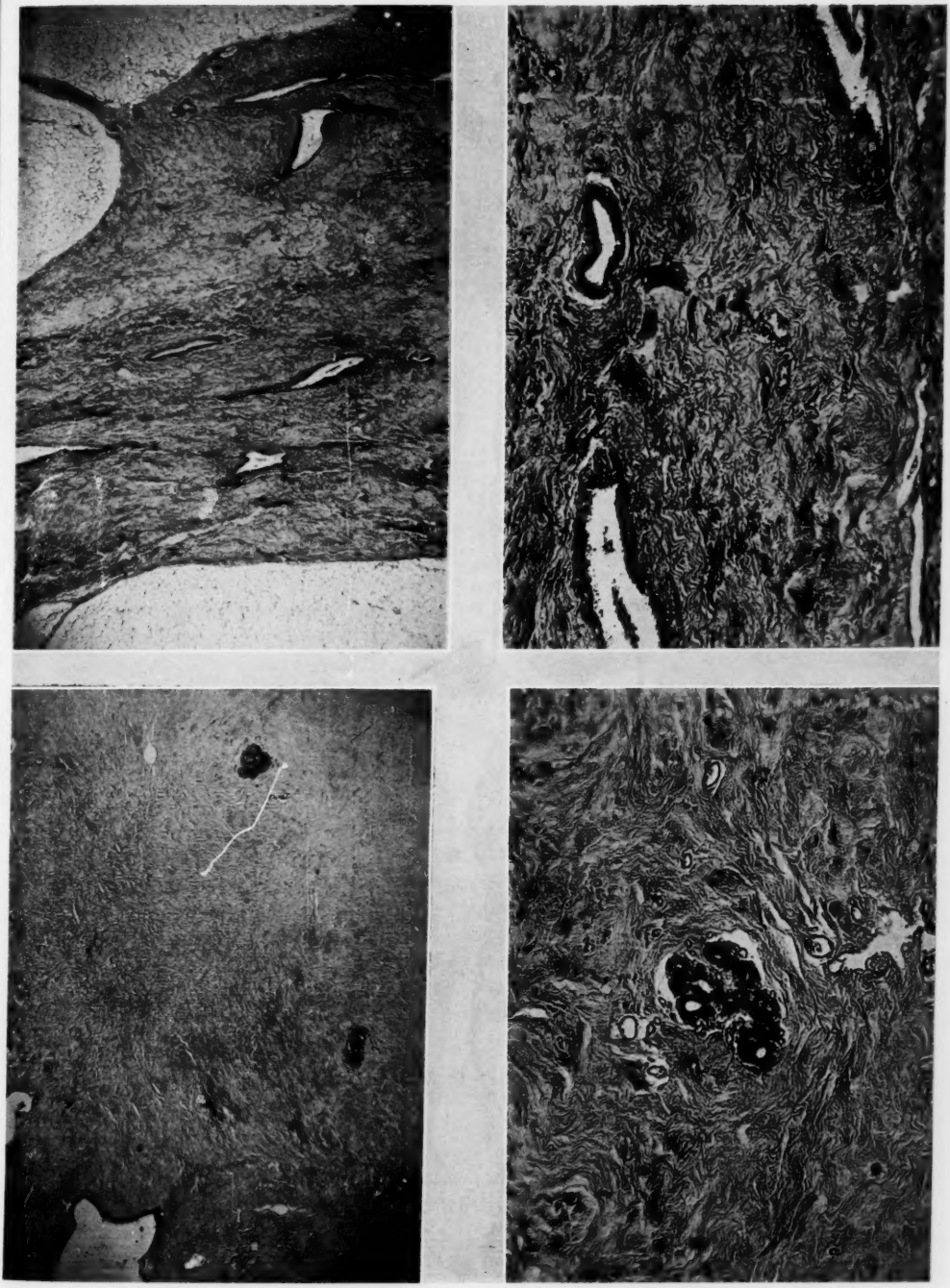


FIG. 11. Normal male breast. Biopsy no. 21. Several ducts lying in a band of moderately dense interlobular stroma. Note loose, fatty tissue. ×20.

FIG. 12. Normal male breast. Biopsy no. 21. Small ducts lying in moderately dense stroma. ×100.

FIG. 13. *Case 20.* Breast biopsy. Two lobular structures embedded in dense interlobular stroma. ×20.

FIG. 14. *Case 20.* Breast biposy. Lobular structure with small ducts and end-buds. No alveoli. Note density of interlobular stroma and small amount of intralobular (periductal) stroma. ×100.

DISCUSSION

The progressive decline of spermatogenic activity which occurs in the testis may be due to the initiation of sclerotic changes in the lamina propria and therefore be related to a reduction in vascular supply to the tubules. Since the avascular seminiferous epithelium is dependent for its nutrition upon the diffusion of materials through the lamina propria from the neighboring capillaries it is apparent that sclerotic changes in the surrounding connective tissue would impede that process. In the syndrome under discussion the extensive hyalinization would tend to accentuate this obstruction and result in the rapid and complete cessation of spermatogenic activity. In simple fibrosis testis the same final result occurs as a part of the aging process, but the change is less extensive and appears to proceed at a much slower rate. In our attempts to explain the occurrence of hyaline sclerosis we have entertained the idea that it might be due to trophic disturbances. In some testes we have seen sclerosis of the media in many of the large sized and medium sized vessels and an unusual thickening of the media with narrowing of the lumen in smaller arterioles. However, these changes do not appear to be severe enough to account for the stromal and parenchymal damage nor are they present in every testis. It is more likely that these vascular changes are secondary effects and may follow or accompany rather than precede the tubular damage.

The concept outlined above would suppose that the primary damage resides in the stromal elements and relegates the decline in spermatogenic activity to a secondary effect. This would agree with the observations of Sand and Okkels (16) who studied the testes of 65 men who were castrated or died suddenly between the ages of 30 and 40 years. They remark upon the fact that the text-book picture of the normal testes is the exception rather than the rule among young men regarded as medically normal. In only 17 of their cases was the condidition of the testis considered to be normal. In the remainder they described moderate or severe damage to the seminiferous epithelium accompanied by thickening of the lamina propria. They believe that the damage to the seminiferous epithelium may be secondary to the process of peritubular fibrosis.

On the other hand Charney and Meranze (6) and Oberndorfer (15), in calling attention to the constant appearance of fibrosed tubules in the testes of patients with severe systemic inflammatory conditions, suggest that the fibrosis as secondary to degenerative changes in the germinal epithelium. Mott (17) in his discussion of the testicular degeneration which is observed in dementia praecox has described changes in the tubules which are similar to those seen in the Klinefelter syndrome. No similarity, however, exists in the condition of the Leydig cells. Mott regarded the peritubular fibrosis as secondary to degenerative changes in the germinal epithelium. Furthermore, various authors (Odiorne and Simmons, 18; Cooper, 19; Wangensteen, 20; Smith, 21) have called attention to the fact that peritubular fibrosis, with hyalinization of the basement membrane in some instances, and intertubular fibrosis are seen regularly in undescended testicles of adult men. Since it is probable that the higher temperature to which such testes are subjected affects the germinal epithelium directly the stromal changes would seem to be secondary in cryptorchidism. It is true that the germinal epithelium would seem to be a more sensitive tissue than the connective tissue elements of the lamina propria and would thus tend to be affected more readily by damaging influences.

In the group of patients we have described there has been no single factor or combination of factors which can be invoked to explain the early decline of the testes. Furthermore, none of the patients presented a history of severe inflammatory disease and in each instance the testes, although very small, were situated well within the scrotum. It is possible that the condition represents a form of constitutional defect which becomes manifest during puberty or adolescence and results in complete atrophy of the seminiferous epithelium. Although our observations do not enable us to speak with complete assurance on the matter we are inclined to believe that the atrophic changes in the germinal epithelium are secondary to sclerosis of the basement membrane and lamina propria.

We have interpreted the various observa-

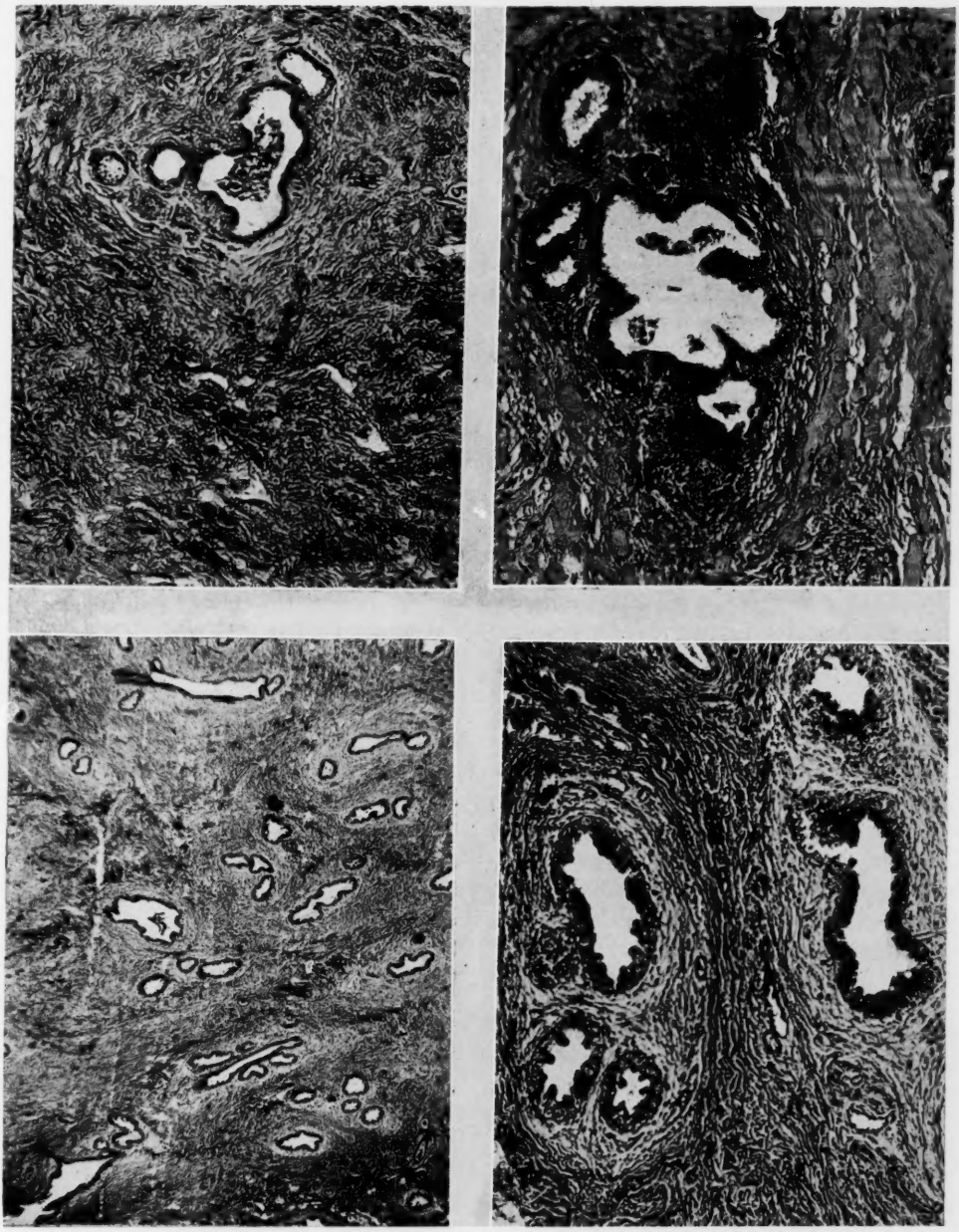


FIG. 15. *Case 15.* Breast biopsy. Small ducts in moderately dense stroma. No increase in periductal connective tissue. ×100.

FIG. 16. *Case 5.* Breast biopsy. Large and small ducts and alveoli present. Interlobular stroma dense. Increased periductal and intralobular connective tissue. ×100.

FIG. 17. Puberal gynecomastia. Breast biopsy no. 127. Numerous ducts arranged in lobular patterns. Moderately dense interlobular stroma. Increased periductal and intralobular stroma. ×20.

FIG. 18. Higher magnification of breast from no. 127. ×100.

tions on the Leydig cells as indicating functional failure of these elements. In most of the testes the evidence seemed to point to a widespread transformation of Leydig cells to fibrocytes and fat cells (fig. 6). These latter two types of cells were far more abundant in every biopsy than in the testes of normal men and in most instances intermediate stages could be identified without difficulty. These stages involve a progressive decrease in cellular size, loss of granulation, change in cellular shape, and change in nuclear conformation. In addition, such testes always show a marked increase in the number of intertubular connective tissue fibers.

Other changes which we have regarded as indicative of failure of the Leydig cells include the loss of birefringent material and decline in the character of the Schultz reaction for cholesterol. Although the precise relation of the substances which are revealed by these tests to the function of the Leydig cells is uncertain we believe that the observations may be regarded as supplementary evidence. It is true that some of the testes, notably in *Cases 1*, *2* and *3*, which are considered to be examples of severe failure, do show strong birefringent and Scultz reactions. However, in each of these instances the strongly positive character of the tests appears to be due, in part at least, to material in cells which are undergoing such degenerative changes as vacuolation and transformation to fibrocytes or fat cells. In normal testes and, indeed, in the testes of those of our patients with less evident failure the birefringent and Schultz-positive material is confined principally to cells which are considered to be functional Leydig cells. However, we are unwilling to place undue emphasis upon the results of these tests and offer them as supplementary evidence, only. The observations on Sudan and osmicated preparations have been no more significant although they do tend to confirm the idea that the Leydig cells in the testes of these patients are failing. Of far greater significance have been the studies on granulation. Without exception the Leydig cells have shown a tendency toward agranular states and this finding has been particularly striking in those testes rated as "Failing" in table 1.

The aggregation of Leydig cells in large clumps is due principally to the great loss of tubular material. In a few instances (*Cases 11* and *14*) we have entertained the idea that an actual increase in the number of cells may have occurred. In these cases the clumps were very large and the general picture was less suggestive of degenerative changes in the cells than in the other cases with the exception of patient *No. 20*.

The factor or factors involved in the multiplication or increase of Leydig cells are uncertain. Mitotic figures are rarely seen in Leydig cells and have not been induced with any degree of regularity by experimental procedures. The interstitial cell-stimulating factor is instrumental in producing an hypertrophy of existing cells rather than an actual numerical increase. Since we cannot speculate profitably concerning the factor which effects a transformation of fibrocytes or mesenchymal cells to Leydig cells we cannot satisfactorily explain the reverse process. However, it is possible that we are dealing with a condition in which the production of interstitial cell-stimulating hormone is reduced and that the failing Leydig cells reflect this state. Our studies on the excretion of gonadotrophic hormones are inconclusive as evidence in this regard since the occurrence of luteinization in the ovaries of some test animals may be the result of a participation of the animals' own hypophyses.

The observation that each patient exhibited clinically some departure from the normal which departure could be attributed to reduced amounts of circulating androgen is in agreement with the judgment that the Leydig cells are in a state of functional failure. It is true that the level of excretion of 17-ketosteroids falls within the normal range in some of the patients whose Leydig cells are regarded as failing. However, it is important to recall that the 17-ketosteroid complex is made up of non-androgenic as well as androgenic substances (Dobriner, 12) and that a relatively high level of 17-ketosteroids does not necessarily imply a proportionally high level of androgen. Indeed, it seems probable that the 1:1 ratio between the major components of the complex—androsterone and its biologically inactive isomer aetiocholanone—which is observed in vigorous young subjects has changed markedly in the

direction of an increase in the inactive compound. Such a shift without a decrease in the total excretion has been observed in a variety of conditions, including senility (Dobriner, 12), and probably represents a change in the metabolism of the precursor substances. Since we believe that we are dealing with a form of premature testicular senility in these patients it is not unlikely that the picture of failure in the Leydig cells and the clinical evidence of deficient androgen can be related to a shift in the metabolism of the steroid substances. Some regard must be paid to the participation of the adrenal cortex in the total output of 17-ketosteroids but there is no reason to believe, in the face of the clinical evidence, that cortical contribution to the total of 17-ketosteroids has compensated completely for the presumed decline in Leydig-cell function. However, it is possible that a compensatory participation of the adrenal cortex in the production of androgens has modified to a greater or lesser degree the severity of androgen deficiency—at least in so far as its clinical manifestation is concerned. This would account for the variable clinical status of our patients.

We are not able to explain satisfactorily the changes that have been observed in the breasts of these patients and can only repeat the idea which we have presented in an earlier paper to account for the occurrence of a similar gynecomastia in functional prepuberal castrates (Heller, Nelson and Roth, 11). This explanation suggests that some member or precursor of the 17-ketosteroid complex may have mammogenic activity. It is presumed that this substance, the nature of which is admittedly unknown, is produced in the adrenal cortex and appears only, or occurs in increased amounts, under circumstances which have their origin in failing function of the Leydig cells with subsequent compensatory activity of the adrenal cortex. The observations of Wagenseil (13) on eunuchs who had been castrated early in life are significant. His photographs, taken many years after castration, show in some instances a very evident gynecomastia. We are inclined to explain the mammary development in these eunuchs on the same basis as that offered for our two groups of patients. In these, as in Wagenseil's eunuchs, Leydig cells were either lacking or undergoing functional failure, but adrenal activity continued and presumably carried on some form of compensatory function. We agree with Kleinfelter, Reifenstein and Albright (14) that the microscopic picture seen in the breasts of these patients is unlike that found in men who have received treatment with estrogen. In addition we agree that there is no relation between the levels of excretion of estrogen and the condition of the breasts. However, we cannot accept their explanation for the occurrence of gynecomastia. The latter is based upon the hypothesis that the testis secretes a non-adrogenic hormone, inhibin, which in addition to its action in inhibiting the production of gonadotrophin by the hypophysis also inhibits the mammogenic action of testosterone. The evidence for the existence of inhibin appears to us insufficient and the same holds true with regard to the evidence for a mammogenic activity of testosterone in man. Furthermore, neither Wagenseil's eunuchs nor our functional prepuberal castrates could have been producing either inhibin or testosterone.

Whatever agent or combination of agents is responsible for the changes in the breasts of the patients under discussion, as well as of our functional prepuberal castrates, it is important to emphasize the fact that stromal changes are more marked and more constant than are increases in parenchymal structures.

The general characteristics of the breasts which showed evidence of gynecomastia are similar to cases observed by others in men beyond the years of adolescence [see Geschickter (22) for a recent consideration of the subject]. Such breasts may contain considerable quantities of glandular structures but frequently they are principally fibrous in character. A high degree of correlation between gynecomastia and testicular defects has been noted but no consistent relationship has been demonstrated between the urinary levels of estrogen or androgen and gynecomastia.

SUMMARY

Biopsies of testes and breasts from 19 patients who presented the picture of hyalinized seminiferous tubules associated with high urinary gonadotrophins have been studied in de-

tail and compared with material from men regarded as normal.

The primary defect in the testes of these men is in the seminiferous tubules in which progressive sclerosis of the lamina propria and basement membrane and retardation of spermatogenesis occurs. The end result of this process is progressive and complete disappearance of all germinal and Sertoli cells and complete hyalinization of the tubules.

Leydig cells present a variable picture. In most testes they show an apparent, but probably not actual, increase with a tendency to form large clumps. Fibroblasts and fat cells are increased markedly in most testes and the impression is distinct that these types are increasing at the expense of Leydig cells. From a cytological standpoint the latter present a variable picture but in most instances they appear to be undergoing functional failure. It is possible to correlate the condition of the Leydig cells with the clinical condition of the patients and, in a general fashion, with the output of 17-ketosteroids.

The stromal and parenchymal changes in the breasts can be correlated in some, but not all, cases with the gross appearance of the breasts. In general, an increae in the amount and density of the stromal elements is the most constant finding. It is presumed that the changes in the breasts are related to a disturbance in the metabolism of steroid hormones subsequent to failure of the Leydig cells.

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Hyalinization of Seminiferous Tubules and Clumping of Leydig Cells. Notes on Treatment of the Clinical Syndrome with Testosterone Propionate, Methyl Testosterone and Testosterone Pellets[1,2]

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FIFTEEN of the cases described in the companion papers (1 and 2) were available for treatment. Therapy was deemed advisable for some because of their eunuchoidism, for others because of their climacteric symptoms but for most because of their lack of vigor and subnormal muscular strength. Those with marked gynecomastia, but with otherwise fairly normal development, were given androgenic therapy in order to gauge its effect upon the excessive breast development.

Therapy consisted of daily injections of testosterone propionate[5] given intramuscularly 5 times weekly to 14 of the 15 subjects. Methyl testosterone was administered sublingually in the form of specially compressed tablets or in the form of a liquid (dissolved in propylene glycol) in several instances. Implantation of 6 to 8 free testosterone pellets, weighing 75 mg. each, was undertaken in 5 cases.

In four instances determinations of the gonadotrophic excretion before, during and after therapy were made.

RESULTS

The eunuchoidal group. Four individuals in this group (*Cases 1* through *4*) were given androgenic therapy. *Case 1*,[6] age 25 years, has received several courses of testosterone propionate in doses of 25 mg. 5 times weekly over a three-year period. During this time a number of striking changes have occurred, and are listed in approximate order of appearance. Change in pitch of voice from high to normal, increase in the number of erections from 1 to 2 per month to 2 daily, production of ejaculation, increase in length of penis from $1\frac{1}{2}$ inches to $3\frac{1}{2}$ inches, change in the pubic escutcheon from female to normal male, and formation of axillary hair were among the early changes seen within weeks to months. Development of normal amounts of hair upon the previously hairless extremities, on the body and upon the face

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[5] The testosterone propionate (Oreton), methyl testosterone in propylene glycol, and the free testosterone pellets (Oreton-F pellets) were supplied through the courtesy of Mr. George Straayer and Dr. Max Gilbert of the Schering Corporation. The methyl testosterone tablets (Metandren Linguets) were supplied through the courtesy of Dr. Oppenheimer of the Ciba Pharmaceutical Products Company.

[6] Case numbers refer to the patients listed in the two preceding articles in this issue.

(shaves every second day); and slight recession of scalp hair occurred only after 2 years of treatment. The most interesting change occurred in the psyche. This lad was initially shy, reticent, embarrassed, irritable, lost his temper easily, was extremely nervous, and utterly without ambition. Within 2 weeks after therapy was initiated all the above characteristics were completely banished and the lad was gainfully employed for the first time in his life, later studied a trade, and is now performing essential war work. Just as striking was the increase in muscle mass and strength.

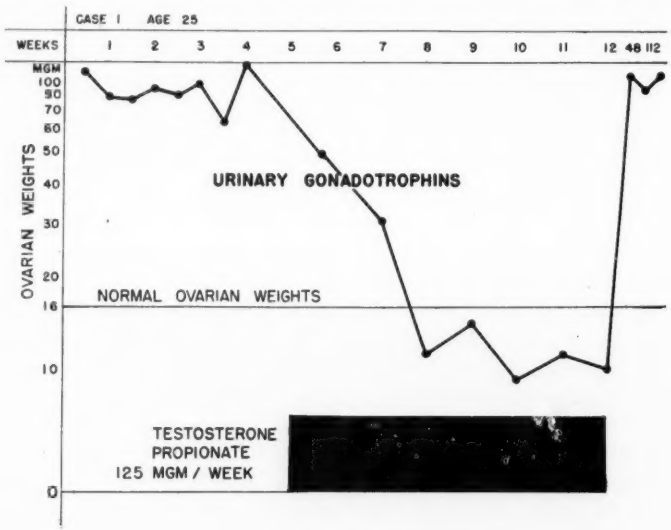

CHART I

Prior to therapy he was constantly fatigued and had subnormal muscular development and strength; after treatment he was able to endure 8 to 12 hours of work daily without fatigue and showed marked increase in muscle mass and strength, as reflected in the gain of weight from 117 pounds to 150 pounds without clinically demonstrable gain in fatty tissue. Another noteworthy feature of this patient's response to treatment was the rather immediate reversal to the former personality pattern and loss of strength that occurred within 3 weeks after therapy was withdrawn. Treatment was interrupted several times and on each occasion a profound relapse occurred, followed by prompt remission when therapy was resumed. The response of the urinary gonadotrophins is recorded in chart 1 before, during and after the first course of testosterone propionate injections. Note that gonadotrophins fell to normal levels during treatment, only to rise again when treatment was discontinued. After 6 months of vigorous therapy it was possible to reduce the dosage and maintain control with a minimum of 25 mg. of testosterone propionate, given intramuscularly, twice weekly. Substitution of oral doses of 100 mg. of methyl testosterone per day did not maintain this patient in remission. A trial of methyl testosterone tablets given sublingually also failed to maintain the remission and in addition produced anorexia, nausea, headaches, vertigo and weakness of the legs. Six months ago six 75 mg. pellets of testosterone were implanted under the skin of the thighs. An immediate and striking response occurred. The patient stated he has never been as well and his family commented that he has never been as easy to get along with as during the months following the pellet implantation. Gonadotrophin excretion during this period did not drop (chart 2) as it had previously during the injection therapy, although the clinical response was as good, if not better. This clearly indicates that the effectiveness of the hormone

is not mediated through pituitary suppression. To our surprise, the effect from the pellets has persisted for 6 months.

Case 2, age 18 years, who was also judged clinically to be completely eunuchoidal in habitus and infantile in sexual development, responded well to testosterone propionate, which was injected 5 times weekly for 5 weeks. The voice became deeper; the penis and scrotum enlarged; erections, which had previously occurred 2 or 3 times daily, now occurred 20 times daily; pubic hair increased slightly in amount; and enuresis, which had been present since childhood, disappeared. The patient stated that he was stronger and more alert, but still tired easily.

During the following 8 months, 50 mg. of methyl testosterone in propylene glycol was administered sublingually every day. At the interview 3 weeks after beginning this regimen, he complained of anorexia, bitter taste of the medication and swollen gums. Erections were less frequent. Upon continuing the sublingual administration, the anorexia and soreness of the gums disappeared, but with annoying frequency heart-burn and eructations followed taking the medication. Evaluation at the end of 8 months of therapy showed that only slight changes in secondary sex characteristics had occurred since the initial injections. The gains made with testosterone propionate were maintained (although enuresis recurred) and in addition the scrotum and epididymis enlarged and pubic hair developed somewhat. After implantation of eight 75 mg. pellets of free testosterone the enuresis disappeared, the pubic and axillary hair grew rapidly, the penis and scrotum enlarged further, the voice deepened more and became more resonant. He again felt more alert and he stated he was less easily fatigued. At the end of 4 months, adequate androgenic activity was still apparent.

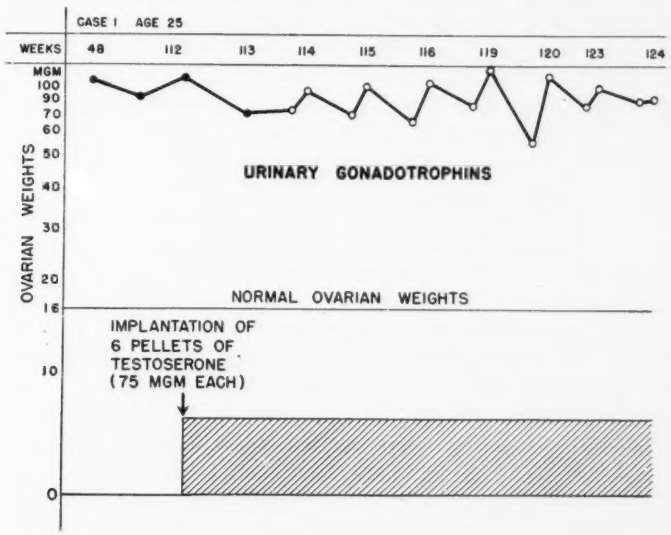

CHART II

Case 3, age 55 years, was admitted to the wards of Receiving Hospital because of acute abdominal pain and backache. In addition, he complained of hot flashes, paresthesias, muscle pains, blurring of vision, vertigo, headaches, nervousness, fatigue, nocturia and impotence. Complete physical examination, x-ray studies and laboratory studies failed to reveal any organic cause for his complaints. The diagnosis of the male climacteric was then entertained along with the recognition of his eunuchoidal state. A total of 16 injections of 25 mg. each of testosterone propionate were administered during a three weeks period. All of the above symptoms vanished by the end of one week and erections returned promptly to occur 3 or 4

and efficiently. His voice was also more resonant and clearer, although not deeper. Most of these desirable changes occurred despite the individual's own estimate prior to treatment that he was entirely normal and desired no change.

One of the patient's major early accomplishments, illustrating his change in attitude and his increase in strength, was to protect his mother from a beating by his drunken father by administering a beating to the father.

The patient maintained all his improvement during a two-month period without treatment and was accepted by the Army. He was seen on furlough after 4 months of most rigorous Army training. He was one of 50 men of an initial group of 200 who were able to respond satisfactorily to a particularly vigorous special program. In the course of his training he had qualified as an expert in marksmanship with rifle, pistol and machine-gun. He illustrates well the maintenance of therapeutic effect after cessation of treatment. This was seen in most cases having this syndrome.

Case 10 failed to exhibit any beneficial effects from either sublingual or intramuscular therapy other than increase in amount of hair and in the size of the genitalia. In fact, the methyl testosterone linguets (50 mg. daily for one month) caused anorexia, nausea, occasional vomiting and weakness of the legs.

Case 13 likewise noted no changes during treatment with testosterone propionate. This was not continued sufficiently long to judge its effect upon hair growth.

Case 11 exhibited marked improvement continued progressively for 6 months following implantation of 8 testosterone pellets.

The normal group. The four patients were given testosterone propionate intramuscularly in 25 mg. doses 5 times weekly in order to gauge the effect upon their pronounced gynecomastia. Since all four were obese they were also placed upon a reducing diet. All lost weight and all had some degree of reduction of fat in the breasts. In no instance, however, was there any marked reduction in the gynecomastia. In fact, the areolae and nipples were stimulated to grow and to acquire darker pigmentation during the period of androgenic treatment. Similar changes in the areolae and nipples were observed in patients whose breasts had been normal prior to therapy. In *Cases 4, 6* and *15*, who had slight gynecomastia, testosterone produced a definite increase in the amount of mammary tissue.

To our surprise, all four subjects in the normal group claimed the following beneficial effects during testosterone treatment: a feeling of well being, reduced nervousness and irritability, increased vigor and strength and increased potentia. *Cases 17, 18* and *19* had further growth of hair on the face, trunk, abdomen and extremities.

Urinary gonadotrophins were depressed by the injection therapy in all four cases in which they were studied. This series includes cases from each group (*Cases 1, 6, 18* and 20). Chart 1 illustrates this response.

DISCUSSION

The order of response to androgenic therapy usually progresses in a step-wise fashion, recapitulating the order of progression observed during normal maturation.

This same order of progression is seen with therapy in the several types of prepuberal hypogonadism we have had occasion to study. The latter includes individuals with functional prepuberal castration, hypogonadotrophic eunuchoidism and the group under discussion. *Case 1* illustrates this response. Early responses usually include genital growth and development of pubic and axillary hair. This begins as early as one week after therapy is instituted and continues for several months. Development of body and facial hair usually does not occur until after 2 to 3 years of continuous treatment.

It was especially interesting, therefore, to find that the subjects in the moderately eunuchoidal and normal groups, who already had normal or nearly normal development of the genitalia and of the pubic and axillary hair, had early responses in the development of body and facial hair. Stimulation of hair growth in these sites was often demonstrable in the normal group within one month of the initiation of treatment. It is apparent from this that one can intervene, with androgenic therapy, at any point in the maturation process

times daily. In addition, the patient gained 17 pounds in weight and experienced a feeling of well being. These gains were maintained to a great extent for several months without further treatment.

Case 4 received 25 mg. of testosterone propionate 5 times weekly for 8 weeks. He exhibited an excellent response, comparable to those described in detail in *Cases 1* and *2*. After 38 injections, the sublingual administration of methyl testosterone liquid was substituted. Three weeks after receiving 50 mg. daily he experienced nausea and vomiting following each sublingual dose. This stopped upon discontinuing the drug, only to recur after resuming therapy. Flatulence associated with abdominal pains was noted along with the nausea and vomiting, and occurred within one hour after each dose. The number of erections decreased from 10 to 1 daily, were not sustained, and were associated with premature ejaculation as opposed to sustained erections and normal ejaculation while on the injection program. Good results were obtained and further progress resulted from a course of testosterone propionate, 25 mg., given intra-muscularly thrice weekly. In contradistinction to *Case 1*, after therapy was stopped all gains continued. After one year without treatment the patient was sufficiently confident in himself to marry.

Each patient became more interested in sex and each patient became generally aggressive. It is interesting that the sex interest and general aggressions followed different patterns, dependent, it seemed, upon the family background, environment and sociological pattern developed before the treatment was instituted. *Cases 1* and *2*, whose background and family ties were those of average, lower-middle-class families, developed an interest in girls and had occasional social engagements to escort girls to the movies. They expended their aggressions in performing war work. *Case 3*, a Detroit slum Negro, indulged himself in a continuous sex orgy and apparently had no need to let out his aggressions in any other way. *Case 4* had been a drifting, unskilled worker who participated in tavern brawls and was invariably beaten up. After his aggressions developed he continued to participate in tavern brawls, but usually was on the winning side. It was strongly suspected that this patient had been an active combatant in the recent disgraceful Detroit race riots and as a consequence all further therapy was suspended.

The moderately eunuchoidal group. The indication for treatment was plain in *Cases 9* and *14*, who had outspoken climacteric symptoms. In each case a satisfactory response was obtained by administering 25 mg. of testosterone propionate per week. However, even more satisfactory results occurred after the implantation of 6 pellets of free testosterone. The effect in both cases has continued for more than 6 months since the implantation.

The indication for androgenic therapy was not as obvious in the five other cases of this group, who were available for treatment (*Cases 6, 10, 11, 13* and *15*). One of the prominent stigmata of eunuchoidism in these patients was the skeletal disproportion, but since the epiphyses were closed this obviously could not be altered. The voice appeared to be normal, erections and ejaculations were satisfactory, the size of the genitalia was normal (except in *Case 10*). There was delay in development of adult-type, male distribution of hair, but this was of no concern to the patients. They were equally unconcerned about the lack of facial hair and considered the infrequent shaving a blessing. In each instance the patient judged his own strength and endurance to be normal. All five had been rejected for military service because of psychoneurosis. Muscular development and strength were judged by the authors to be inadequate and androgenic therapy was therefore used to improve it and to gauge the effect upon their personalities.

Case 6 typifies the response obtained in three subjects (*Cases 6, 11* and *13*). He received a total of 60 intramuscular injections of testosterone propionate given 5 times weekly. At the interview after 4 weeks of therapy a weight gain of 16 pounds was noted (apparently not fat), erections had increased in number, the penis was larger, and there was increase of fuzz on the face. Patient stated that he was less nervous and felt stronger and more alert. He commented, "I have a better appetite than I ever had in my life . . . and never felt so good before." He also volunteered that he could think, speak and perform more rapidly

delay in maturation, constitute the majority of the cases in this syndrome. In our own experience we have found the greatest number of cases at the induction center when we have personally examined inductees with the idea of discovering additional examples. Our successful experience with the treatment of these patients leads us to urge that the syndrome should be looked for since the benefits of therapy which accrue to the patient are great and usually are quite unanticipated.

SUMMARY

It was found that patients suffering from hyalinization of the seminiferous tubules with partial Leydig-cell failure responded favorably when treated by substitution therapy with androgens. These satisfactory responses included the following: 1) correction of sexual infantilism in those instances where it occurred; 2) initiation or acceleration of the maturation process in those instances where it had been found to be incomplete; 3) relief from symptoms of the male climacteric, the latter occurring frequently in subjects over 25 years old; 4) surprising improvement of the psyche and of muscular development and strength in the majority of cases. The favorable responses often could not be anticipated on the basis of the clinical evaluation of the patient prior to the introduction of therapy.

Implantation of 6 to 8 pellets of testosterone, weighing 75 mg. each, under the skin was the most satisfactory method used. The effect of a single implantation lasted 6 months or longer. The injection of 25 mg. of testosterone propionate 5 times weekly was also successful. The effects of methyl testosterone administered orally or sublingually were disappointing.

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and expect the response to follow the same orderly and progressive pattern.

Indications for androgenic therapy in the subjects suffering from the syndrome were arrived at from the responses obtained. The eunuchoidism and sexual infantilism obviously merit treatment and the results were uniformly satisfactory. In those instances in which eunuchoidism and infantilism were not clinical problems, therapy was still indicated because of the very marked and highly desirable effect upon the psyche, muscular development and strength and the increased efficiency resulting therefrom. In some instances these effects have amounted to the complete social and economic rehabilitation of the patient. Often it has been impossible to predict that these beneficial effects would follow institution of therapy, and we therefore suggest that all instances of the syndrome should have the benefit of a trial with testosterone. The climacteric symptoms that not infrequently are an accompaniment of the syndrome, after the age of 25 years, respond dramatically to appropriate substitutional therapy. Gynecomastia is not affected by androgens and if excessively bothersome, either anatomically or psychically, we believe that surgical removal is advisable.

Choice of androgenic preparations. Testosterone propionate given in 25 mg. amounts subcutaneously or intramuscularly five times per week is a satisfactory therapeutic agent. However, the implantation of 6 or 8 pellets of testosterone, weighing 75 mg. each, under the skin is the most efficient, convenient and all-around satisfactory means of treating these patients. Methyl testosterone given orally or sublingually has not proved to be a useful clinical measure and in some instances has been associated with undesirable reactions.

Should chorionic gonadotrophins be used? We have not attempted this type of therapy to date and therefore are not in a position to give an unequivocal answer. One can, however, infer from the elevation of total gonadotrophins in the urine and the luteinization reaction elicited in the test animals that the patients have either a normal or supranormal amount of circulating luteinizing hormone and additions of chorionic gonadotrophins would not be helpful. At the same time it can be stated that androgenic therapy is not harmful since, with the exception of one case, withdrawal of therapy was followed by maintenance or actual increases of the beneficial effects. Thus androgens did not permanently suppress function of the Leydig cells, and may have increased their activity in some unexplained manner.

Therapeutic evidences of Leydig-cell failure. In some of the cases clinical examination, microscopic appearance of the Leydig cells and excretion of 17-ketosteroids, if evaluated separately, would suggest that the Leydig-cell function was normal. However, when these three criteria were evaluated together the conclusion was reached that in no case was the Leydig-cell function entirely normal. The therapeutic response lends further credence to this concept since each subject in whom any doubt existed concerning the functional state of the Leydig cells derived beneficial effects from androgenic therapy. Normal men similarly treated do not experience such beneficial effects. Thus we infer that the function of the Leydig cells was subnormal in our patients.

Importance of the syndrome. We feel that this is an important syndrome since it apparently occurs frequently and because such patients respond well to treatment with testosterone. Of all the recognized forms of male hypogonadism, in our experience this syndrome is by far the most frequently encountered. Such a statement may seem paradoxical when one considers the infrequency with which it has been recognized in the past. This is understandable, however, when one considers that these patients rarely seek medical advice for relief of their endocrine abnormality. Only one subject received medical attention for his eunuchoidism and two others attracted attention because of their climacteric complaints. In all others the discovery of the endocrine deviations from normal coincided with the performance of physical examinations for other reasons, in the main, as part of the pre-induction physical examination for entry into the armed forces. This syndrome can easily be overlooked even upon careful physical examination since most of the subjects have a superficially normal appearance. This is especially true of the moderately eunuchoidal group who, although they have neither pronounced gynecomastia nor marked

Vaginal Cornification Phases During Pregnancy

Their Prognostic Significance

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IN PREVIOUS publications (1, 2) attention has been called to the utility of vaginal smears for the quantitative estimation of ovarian hormogenic activity. The production of estrogen and progesterone may vary from none to normal, resulting in vaginal smears that can be graded from 1+ to 7+, depending upon the degree of cornification that appears.

Theoretically, the corpus luteum of pregnancy should disturb the estrogen-progesterone ratio observed in the normal non-pregnant female, causing a shift toward the progesterone side. If this were so, the degree of vaginal cornification during pregnancy might be expected to be less than that found in the normal non-pregnant woman. Therefore, if during pregnancy one discovers the same high degree of vaginal cornification that is associated with the normal non-pregnant state, one could conclude that progesterone production is inadequate and that progesterone or pregneninolone therapy is indicated.

To check the validity of this hypothesis, vaginal smears from a number of pregnant women were taken at weekly intervals throughout gestation. The first small group observed had been under treatment for hypo-ovarian sterility. In attempting to improve ovarian function we routinely follow the effects produced by estrogen-progesterone, or gonadotropic administration, by means of frequent vaginal smears. Consequently, it was not difficult to continue taking smears at weekly intervals after the first "missed" period. The importance of this was soon demonstrated and this procedure is now followed during the care of all pregnant women under our supervision. During the first two to four weeks of pregnancy the degree of vaginal cornification remains rather high in all of those examined. Promptly thereafter the great majority show a 4+ phase or lower. For illustration of the appearance of smears of this and other grades see Hall (1). When, in our experience, uterine cramps or staining have occurred, signifying the probability of abortion or miscarriage, the vaginal cells invariably have been of a high estrogenic phase, while in no case in which the vaginal smear level has stayed at 3+ or lower has difficulty been encountered. No patient who complained of nausea and vomiting aborted or miscarried unless estrogens were administered, a procedure which resulted unfortunately for two patients. Incidentally, percentages of normal or disturbed functional findings are of no relative importance in this study because most of these patients came under our care because of some previous difficulty such as barren marriage, unavoidable abortion or miscarriage, or ovarian hypo-function. Therefore, a greater number of pregnancy disturbances would be expected in this series than occurs routinely in obstetrical statistics. The findings are therefore not presented as statistical percentages but as being significant regarding the possibility of obtaining information early enough to allow treatment that might reduce the number of abortions and miscarriages.

If we assume that some unavoidable abortions or miscarriages are due to a corpus-luteum deficiency, then it would seem that weekly vaginal smears taken during those early months will provide early criteria for beginning therapy. If there is no improvement during

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treatment of these conditions with progesterone or anhydrohydroxyprogesterone then one can assume that other etiological factors are mainly responsible.

Administration of progesterone and/or anhydrohydroxyprogesterone[2] (pregneninolone) when the degree of cornification is above a $3\frac{1}{2}+$ phase seems to have prevented further disturbance in all but three of our patients. These three came to our attention for the first time because of bleeding during pregnancy. Each of these women miscarried in spite of treatment. We are therefore of the opinion that vaginal smears give information sufficiently early to allow successful therapy for those whose probable losses would have been due to a corpus-luteum deficiency but are of no clinical value when the disturbance has progressed to the point of definite bleeding.

Over a period of five years, several hundred pregnant women have been examined at varying intervals, 97 of these at weekly intervals throughout pregnancy.[3] The results in six cases are tabulated herewith as being typical of the variations encountered.

One woman, "*F. H.*," age 27, Para 2, Gravid 2, had such varying findings, and the levels of vaginal cell development changed so frequently, that it was considered to be advisable to present the weekly photomicrographs (for 22 weeks) as illustrative of the apparent practical value of this method of study (see accompanying figure). Apparently the higher estrogenic phases of the vaginal epithelium were quickly changeable by the administration of progesterone or its equivalent.

During the past few months the intervals of taking smears during the sixth to ninth months of pregnancy has been lengthened, if the vaginal cells have remained at safe levels during the previous months.

The probable shortcomings of vaginal smears

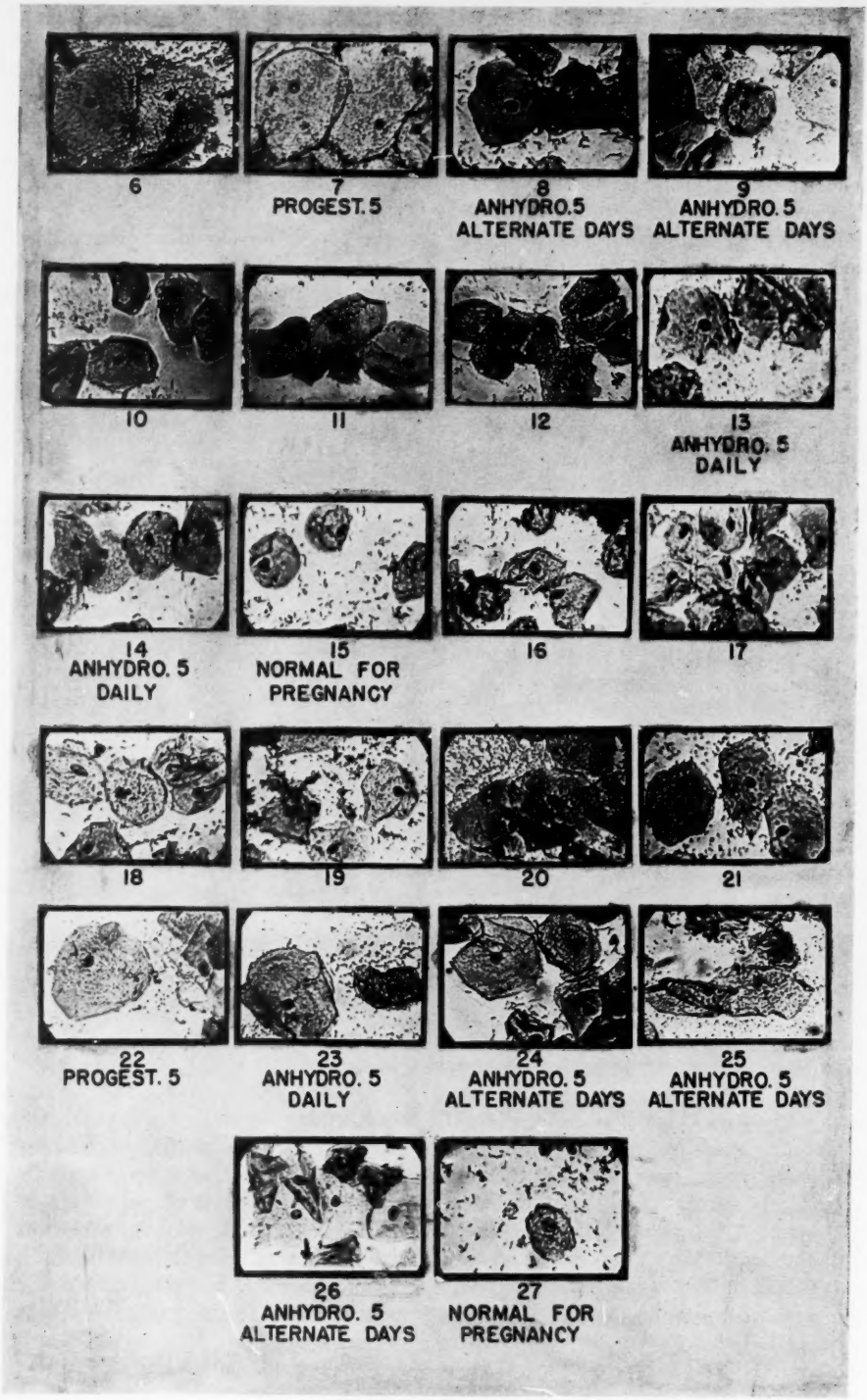
VAGINAL CORNIFICATION LEVELS AND TREATMENT USED DURING PREGNANCY

Week of Preg.	Mrs. E.R. Age 29 Para 1 Gravid 1		Mrs. B.S. Age 25 Para 1 Gravid 1		Mrs. F.H. Age 27 Para 2 Gravid 2		Mrs. A.O. Age 24 Para 2 Gravid 3		Mrs. N.S. Age 34 Para 1 Gravid 1		Mrs. V.B. Age 31 Para 1 Gravid 1	
	Smear	Treatment[1]	Smear	Treatment	Smear	Treatment	Smear	Treatment	Smear	Treatment	Smear	Treatment
6	3+–5½+	(3)	3½+–4½		5+				5+	(1)	5+	(1)
7	4½+	(4)	4½+	(5)	5+	(1)	3+		4+	(1)	4½+	(1)
8	3½+–4½+		3+–5+	(4)	4+	(3)	3+		3½+		4+	(1)
9	4+		3½+–5	(1)	3½+	(3)	3+		4+		4+	(1)
10			2½+–5	(4)	3½+		3+		4+		3½–4½+	(3)
11	4+		2½+–5	(3)	4+	(1)			4½+	(3)	4+–5+	(1)
12	4½+	(4)	3+–4½	(1)	3½+		3+		4+		4+–5+	(5)
13	2+–5+	(4)	3½+		4½+	(4)	3+	None Required	5+	(2)	4+	(1)
14	2+–4+		3½+		3½+	(4)	3+		4+	(3)	4+	(2)
15	3½+		3+–4+		3+		3+		4+		3+	
16	3½+		3½+		3+		3+		4+		3½+	(1)
17	3+		3½+		3+		3+		4+	(3)	3+	
18	3½+		3½+		3½+		3+		3½+		3+–4+	
19			3+–3½		3½+		3+		3+–4+		3+–4+	(1)
20	3½+		3+		4+		3+		3+		3½+	
21	3+		3½+		4+		3+		3+		3½+	
22	3½+		3½+		5+	(1)	3+		3+–4+		3½+	
23	3+–3½+		3+–3½		3+–4½+	(4)	3+		3½+		3+–4+	
24	3½+		3+		3+–4+	(3)	3±		3½+		3½+	
25	3+		3+		3+–3½+	(3)	3+		3½+		3½+	

[1] Treatment:
(1) = 5 mg. progesterone parenterally.
(2) = 10 mg. progesterone parenterally.
(3) = 5 mg. anhydrohydroxyprogesterone orally alternate days.
(4) = 5 mg. anhydrohydroxyprogesterone orally daily.
(5) = 10 mg. anhydrohydroxyprogesterone orally daily.

[2] Pregneninolone (anhydrohydroxyprogesterone), in the form of "Pranone" tablets, and progesterone ("Proluton") used in this investigation were supplied by Dr. Max Gilbert of the Schering Corporation.

[3] It was a privilege to be able to see the slides and summarized case records of 44 other pregnant patients who were under the care of Dr. Anah C. Wineberg of Oakland, California.



Vaginal smears from Patient F. H. age 27—Para, 2; Gravid, 2.

These were taken weekly from the 6th through the 27th week of pregnancy. The smears remained within normal limits from the 27th week until delivery. Abbreviations: 6=6th week of pregnancy, (etc.); progest.=progesterone; anhydro.=anhydrohydroxyprogesterone.

as indication of degrees of ovarian function are understood but this simple, quick technic, and the various phases previously described, seem to be sufficiently accurate to justify its use by all physicians who care for obstetrical patients. In all we have followed 97 cases throughout pregnancy with repeated vaginal smears and have found invariably that a highly cornified vaginal smear is a sure indication of approaching difficulty. These findings are presented as a new method of a quick laboratory test that will aid in preventing unavoidable abortions or miscarriages when due to a low progesterone level.

SUMMARY

Findings have been presented that seem to prove that there is a definite relationship between progesterone secretion and the phases of vaginal cornification during pregnancy. If there is an adequate development of the corpus luteum of pregnancy, the vaginal cells show a low estrogen level, and many can be found that have been called "pregnancy cells" by Papanicolaou (2). Practical use of this knowledge has been made over a period of five years, by making weekly vaginal smears throughout the period of gestation. When the cells were indicative of a high-estrogen phase of cornific action the administration of progesterone or its equivalent seemed to balance the estrogen-progesterone ratio required for normal pregnancy, and abortions and miscarriages were prevented in all but three of 141 cases studied.

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Absorption of Pellets of Progesterone

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PROGESTERONE is utilized effectively by the body when administered intramuscularly in oily solution, when applied sublingually in the form of hard, easily soluble tablets (1, 2) or when implanted subcutaneously as compressed cylindrical pellets. The latter method presents clinical possibilities which have not been exploited (3) and it seemed advisable at this time to record our data on the absorption rates in humans of pure crystalline progesterone pellets.

In 1938 Deanesly and Parkes (4) reported their results of implantation into rabbits of progesterone tablets 5.1 mg. in weight. Five days after implantation they found full progesterone effect in the uterus of the immature animal which had been sensitized with estrone previously. Lipshütz and Maas (5) gave further proof to the effective utilization of subcutaneously implanted progesterone pellets. Regression of abdominal and uterine fibroids, produced in the female guinea pig by estrogens, was obtained when a tablet of synthetic progesterone was implanted.

MATERIAL AND METHODS

Pure crystalline progesterone pellets were employed.[2] These were machine-made under aseptic conditions and supplied by one manufacturer. The pellets were cylindrical in shape and were prepared in three weights, *i.e.*, 50, 150 and 200 milligrams. The pellets were smooth, yellowish white in color and all of approximately the same density. On recovery the pellets showed slight roughening of the surfaces and a more or less uniform shrinkage in the original shape. The pellets were implanted subcuntaneously in the inguinal region by the following method: the skin was anaesthetized by injection of a few cubic centimeters of two per cent procaine intradermally so as to raise a wheal. A small incision, no larger than one centimeter, was made over the wheal through the skin, exposing the subcutaneous fat. A hemostat was inserted through the incision in the direction of the inguinal canal for a distance of several centimeters. The pellet was then inserted with the hemostat into the preformed groove. The incision was covered with a sterile pad. Healing took place within a few days. Data on the rate of absorption were obtained on fourteen pellets after remaining *in situ* from 35 to 166 days (see accompanying table). The pellets were recovered after surgical removal or when expelled from the wound. The pellets were easily cleaned, dried and reweighed. The nine 50-milligram-sized pellets showed for the greater part that close to 20 per cent absorption per month had occurred (see accompanying figure). The results paralleled those obtained by Warwick and Parkes (6) for 50-milligram pellets implanted in the experimental animal. Ten of the 14 pellets recovered, regardless of size, showed an absorption rate of between 18 and 24.6 per cent per month. It appeared that the rate of absorption was fairly uniform for the first three to four months and then tapered off. This finding paralleled our results with pellets of testosterone propionate (7).

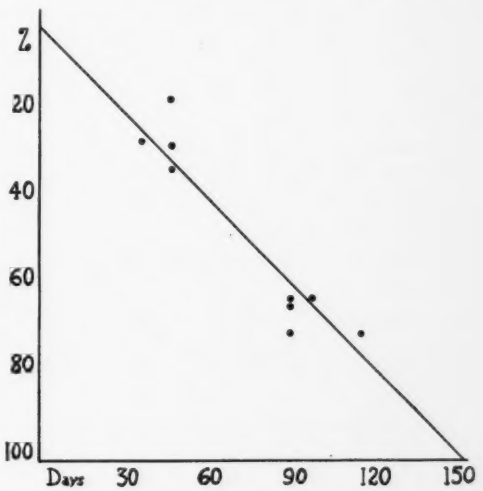
The only available data on the rates of progesterone pellet absorption were provided

[1] This work was completed before the entrance of the senior author into the service. Present address: U. S. Public Health Service.

[2] The pellets of Progesterone used in this study were prepared by Schering Corporation, Bloomfield, New Jersey.

Patient No.	Pellets	Wt. of Pellets		Days in Situ	Per Cent Absorption	Per Cent Absorbed per Month	Per Cent Absorbed per Day	Diagnosis
		Original	On recovery					
1	1	50	36.7	35	26.6	22.8	0.38 mg.	Nervous tension state
	2	50	18.7	95	62.6	19.8	0.33 mg.	
2	1	50	33.2	46	33.6	21.6	0.36 mg.	Habitual abortion
	2	50	36.0	46	28.0	18.0	0.30 mg.	
	3	50	41.2	46	17.6	11.4	0.19 mg.	
3	1	50	13.6	88	72.8	24.6	0.41 mg.	Dysmenorrhea
	2	50	17.7	88	64.6	22.2	0.37 mg.	
	3	50	18.3	88	63.4	21.6	0.36 mg.	
	4	50	14.3	113	71.5	18.6	0.31 mg.	
4	1	200	93.3	166	53.4	9.4	0.63 mg.	Puberal breast hypertrophy
	2	200	91.9	166	54.0	9.7	0.65 mg.	
5	1	150	82.5	73	45.0	18.4	0.92 mg.	Habitual abortion
	2	150	77.0	73	48.6	20.0	1.00 mg.	
6	1	150	67.7	49	54.8	33.4	1.67 mg.	Puberal breast hypertrophy

by Forbes (8) and by Warwick and Parkes (6). The latter concluded that progesterone is absorbed from large tablets implanted subcutaneously at an average rate of about 20 per cent per month. Tablets weighing 50 milligrams thus supply about ten milligrams per month. This conclusion was obtained from pellets recovered from ten goats, six guinea pigs, two rats and one woman. Percentage absorption per month varied from 8.2 to 27.5 for the 19 pellets which they recovered after remaining *in situ* from 30 to 140 days. The pellets weighed from 30 to 85 milligrams originally. Forbes (8) found that it required 88 days for 90 per cent absorption of progesterone pellets implanted in rats while for anhydrohydroxyprogesterone pellets less than 30 per cent absorption occurred in 300 days.



Percentage absorption of nine pellets of 50-mg. size plotted against the line suggested by Warwick and Parkes, *i.e.* of 20% absorption per month.

SUMMARY

Data on the absorption rates of pellets of progesterone subcutaneously implanted in humans were obtained in 14 instances. The pellets were of three sizes, 50, 150 and 200 milligrams.

Of the recovered pellets, nine were of the 50-milligram size, three of the 150-milligram size and two of 200-milligram size. The pellets remained *in situ* from 35 to 166 days.

Ten of the 14 pellets recovered showed that there occurred on the average about 20 per cent absorption per month for the first 3 to 4 months.

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The Vaginal Smear in the Diagnosis of Uterine Cancer[1,2]

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WE ARE presenting evidence that uterine cancer can be diagnosed with accuracy by the vaginal smear. The diagnosis depends upon the identification of cancer cells in the vaginal secretion.

Papanicolaou, in 1928, first recognized cancer cells in the vaginal secretion of women with cancer of the uterus. Since 1941 articles have appeared by Papanicolaou (1) and Papanicolaou and Traut (2, 3); and in 1943 a monograph on the diagnosis of uterine cancer by vaginal smear (4) was published by these two authors. In the same year Meigs *et al.* (5) published results on 220 cases. Since our publication we have studied approximately 600 additional cases and here report on our total group of 813, statistics of which follow.

STATISTICS

Negative smears	635
Positive smears	117
Positive—not completed	6
Suspicious	8
Mistakes	22
Poor smears	25
Total	813
Total error	2.8%
Positive cases called negative	7.1%
Negative cases called positive	2.0%

The method is simple. A nurse or the patient herself can easily be taught to take the smear. A dry pipette, with a rubber suction bulb compressed, is inserted into the fornix of the vagina, the bulb is released and the pipette withdrawn. Vaginal secretion is blown on a previously marked glass slide, fixed while still wet in a solution of equal parts of 95 per cent alcohol and ether and stained by Papanicolaou's method (2, 5).

Diagnosis of the smears is not easy. It is not an office procedure. The individual who makes the diagnosis must be familiar not only with the vaginal cytology as described by Papanicolaou and by Shorr, but must also be able to identify cancer cells in the smear. Training in a laboratory doing this special work is essential.

Detailed criteria for the recognition of cancer cells will be found in publications to which reference has been made. The changes most characteristic of cancer are (1) disproportion in size of the nucleus, relative to the cytoplasm and (2) marked inequality of the nuclear size in a cell group. In the cancer cell, in contrast to the normal, the nucleus frequently fills almost the entire cell; in groups of cancer cells there is marked variation in the size of the individual nuclei and some abnormally large nuclei are found. Endometrial cancer cells appear often in groups. Little cytoplasm is evident and the nuclei are usually hyperchromatic. In cancer of the cervix, cells may be found which bear no resemblance to the normal cells of the vaginal secretion; thus long fiber-like cells or tadpole cells with a rounded head containing the nu-

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[2] Aided by grants from the William F. Milton Fund and Joseph H. Clark Bequest of Harvard University.

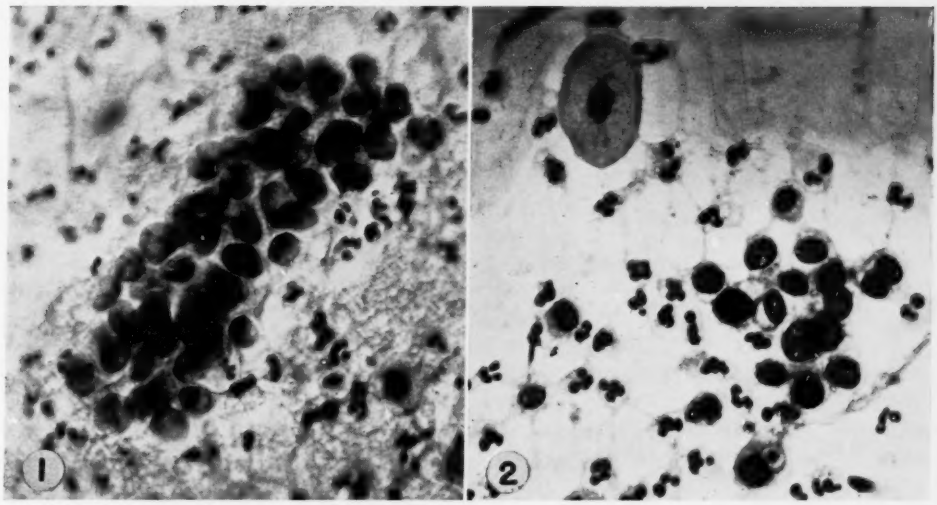

FIG. 1. Positive vaginal smear from a woman of 66, bleeding 2 months. Adenocarcinoma of endometrium. Group of cancer cells. Note presence of large nuclei and variation in size of nuclei.
FIG. 2. Positive vaginal smear from a woman of 60. Only symptom bleeding 2 weeks previously. Cervix appears normal to inspection. Pathological diagnosis: epidermoid cancer of cervix, grade II. (One normal basal cell above.)

cleus and a long thin tail may appear. Blood or blood pigment is found in every positive smear. Leukocytes are present but their number varies (see figures 1 and 2).

The presence of normal endometrial cells and of histiocytes of various types often makes diagnosis difficult. This subject will be fully discussed in a subsequent publication.

A negative smear does not exclude the possibility of cancer but is strong evidence against malignancy. As a positive diagnosis depends upon the recognition of cells desquamated from the tumor, where tumors do not desquamate early, as occasionally happens, the diagnosis will be missed.

A positive smear is presumptive evidence of cancer. Owing to mistaken interpretation an occasional false positive occurs. A positive smear demands immediate biopsy. We do not advise operation on the basis of a positive smear alone.

SUMMARY

From a study of vaginal smears in 813 cases the following conclusions have been drawn.

Cancer of the uterus, even in the early stage, can be diagnosed by vaginal smear.

The method is applicable to the screening of large numbers of women.

A negative smear does not exclude cancer.

A positive smear usually means cancer but fixed tissue diagnosis should precede operation.

A woman with a positive smear should have immediate biopsy even though no clinical evidence of cancer is present.

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Hyperplastic Disease of the Adenohypophysis

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WHILE the pathological morphology of the neoplasms of the hypophysis is largely well known, the hyperplastic changes, which involve the various cell types of the adenohypophysis, as well as the conditions in which they are encountered, might be familiar chiefly to those who have specialized in this field.

The hyperplastic disease of the adenohypophysis may involve either one or more cell types, thus leading to enlargement of the organ, or the hyperplasia of one cell type may take place at the expense of other cell types, in which case the hyperplasia need not result in an enlargement of the organ.

In the following report the conditions associated with hypophysial hyperplasia are discussed in a number of separate sections. To avoid misunderstanding it ought to be initially mentioned, however, that by the term hypophysial hyperplasia only a diffuse proliferation of the glandular elements of the hypophysis with or without cell enlargement is meant.

THE HYPOPHYSIS AFTER CASTRATION

The enlargement of the hypophysis in castrated animals has been known for a long time. The histological picture of the hypophysis in castrated animals is not quite uniform, but the increase in eosinophilic cells is common to almost all mammals. Tandler and Gross (1) were the first investigators to examine the hypophysis in eunuchs as well as in castrated women. The examination was performed partially by x-rays, partially by autopsy. The castration in women is followed, as in experimental animals, by enlargement of the hypophysis with multiplication and heterotopy of the eosinophilic cells and with a decrease in the number of the basophilic cells. In some cases, the castration effect of the hypophysis develops in a very short time, whereas in other cases these changes are not found despite the lapse of many years after castration (Rössle, 2; Berblinger, 3). Castration by x-rays likewise produces, as far as one can tell from the scanty evidence, an increase of eosinophilic cells. There are known only a few cases of congenital absence of the ovaries in which the hypophysis was examined (see Berblinger), and also in these few cases the increase of eosinophilic cells was demonstrable. It is remarkable that the physiological loss of the ovarian function in the climacterium is not followed by hyperplasia of the eosinophilic cells (Rasmussen, 4).

According to Biggart (5), whose statements are in contrast to those made by other authors, the changes in the hypophysis of human castrates are an increase in the number of basophilic cells, the appearance of large chromophobe cells with stages of transition between these and the basophils and, finally a vacuolation and colloid formation in these cells. The response of the eosinophils to the loss of the gonads varies considerably.

Few papers deal with the morphological picture of the hypophysis in castrated males and there are not many reported cases that have been examined thoroughly. The statements are not uniform, since enlargement as well as normal size of the hypophysis, and an increase in the number of eosinophils, or chief cells, are recorded in the literature. By no means do the sparse observations allow the conclusion that the male hypophysis in man responds to castration differently from the female hypophysis. In eunuchoidism, the hypophysis usually shows enlargement with the eosinophilic cells increased in number, but the chromophobes also have been found increased in number and size. The increase of eosinophilic cells has also been observed without enlargement of the

hypophysis. An increase of eosinophils with interstitial fibrosis of the anterior lobe has been described by Herlant (6).

One important fact should not be overlooked, namely, the age of the individual in whom the castration or any other kind of destruction of the gonads had taken place. The younger the individual the more pronounced will be the consecutive change in the hypophysis.

THE HYPOPHYSIS IN ATHYREOSIS AND HYPOTHYREOSIS

A lack of function of the thyroid gland causes hyperplastic changes in the hypophysis. Animal experiments, showing special changes in the hypophysis secondary to thyroidectomy, early called the attention of pathologists to the behavior of the human hypophysis in cretinism, myxedema, and various types of goiter. In cases of congenital absence of the thyroid, or thyroaplasia, which is the cause of the congenital myxedema, the hypophysis as a rule appears enlarged (McCallum and Fabyan, 7; Boyce and Beadles, 8; Wegelin, 9; Kraus, 10; etc.) The increase in size is due to the proliferation of a special cell form which often has been compared with the pregnancy cell. This special cell is larger than the eosinophilic and is more numerous than the basophilic cell. It possesses an ill-defined cytoplasm and a very delicate eosinophilic granulation. Kraus reported a very instructive case concerning a new born baby, 47 cm. in length, who had a total aplasia of the thyroid gland and a marked hypoplasia of the thymus as well as an isthmic stenosis of the aorta with patent foramen ovale, a patent ductus arteriosus, and a defect in the septum ventriculorum, in addition to other malformations. The greatly enlarged hypophysis projected from the sella turcica, like a dark brownred oviform tumor, measuring 13.5×9.5×7.5 mm. in diameter. This enlargement was due to a marked proliferation in the anterior lobe, the cells of which were larger on the average than the chromophils and dominated the histological picture entirely, whereas the chromophilic cells, particularly the eosinophils, were sparse and scattered through the organ in small groups. The chief cells were particularly scanty. The proliferated cells possessed a distinctly outlined cytoplasm, which appeared either well stained, faintly stained or vacuolized. The exceedingly large round or oval nuclei were distinguished by a very delicate chromatin. Specific stains as cresofuchsin, chromium-hematoxylin and azocarmin did not reveal any specific granulation. The stroma of the anterior lobe was delicate and the capillaries greatly injected. Kraus called these cells, that evidently spring from the chief cells, "thyroprival cells," and regarded them as characteristic of thyroaplasia, though not present in all cases. There are cases described neither with enlargement of the gland nor with proliferation of any special cell form. Again, in other cases, there is no enlargement, but there is the characteristic cell proliferation just described (Rocaz and Cruchet, 11). Hyperplasia of the chief cells together with a chromophobic adenoma in the anterior lobe also has been noted by Wegelin (9) who, in two cases, saw multiplication and enlargement of chief cells and adenomas made up of Kraus' transitional cells (evidently the above mentioned "thyroprival cells"). In another case of thyroaplasia, Wegelin found the hypophysis enlarged, hyperemic, and the anterior lobe made up mainly of vacuolized chief cells showing nuclei unequal in size. There seems to be little doubt that these enlarged "chief cells" are also identical with Kraus' thyroprival cells.

In cases of spontaneous myxedema in adults (myxoedema adultorum) observers have described enlargement of the hypophysis, increase in colloid, thickening of the cell cords, enlargement or proliferation of the chromophilic cells, proliferation of chief cells only, or proliferation of all cell types with the chief cells prevailing. In some reports the hypophysis is called normal or only enlarged, but cytologically not altered (Boyce and Beadles, 12; Abrikosoff, 13; McCallum and Fabyan, 7; Berblinger, 14; etc.). In other cases of myxedema, due to fibrous atrophy of the thyroid gland, the hypophysis was found diminished in size, the stroma was thickened, calcium concretions were deposited in the pars intermedia with colloid follicles scattered through the anterior lobe. The glandular cells themselves contained an increased amount of colloid.

In a case of Eichhorst (15) with thyrogenic

dwarfism and myxedema due to hypoplasia and cystic degeneration of the thyroid, the hypophysis was enlarged and showed hyperemia, hemorrhages, hemosiderosis and fibrosis as well as atrophy and necrosis of the parenchyma of the anterior lobe. In a case of pluriglandular insufficiency with myxedema but without cachexia, Castleman and Hertz (16) described fibrosis of the anterior lobe, atrophy of the thyroid and atrophy and lipomatosis of the parathyroid glands.[1]

Just as the animal hypophysis after thyroidectomy undergoes certain changes, so in human cases of post-operative myxedema and thyroprival cachexia the hypophysis is considerably affected. As a rule the hypophysis is enlarged. The histological picture is described by some as showing an increase in the number of chromophils (Langhans, 17), with hypertrophic chief cells exceeding the eosinophilic cells in number (Berblinger, 14). Wegelin, on the other hand, saw enlargement and hyperemia of the hypophysis with preponderance of chief cells and Kraus' transitional cells while the eosinophils were exceedingly sparse. Pyknosis, syncytial clusters of cytoplasm, calcified foci, and large colloid cysts in the pars intermedia are additional findings described. In 5 cases with post-operative hypothyrosis Altschule and Cooper (18) saw an increase in number, size and degree of vacuolation of the basophilic cells and, inconstantly, a slight diminution in the size of the eosinophilic cells. The size and weight of the hypophysis were increased. These authors declared these changes were similar to those observed in patients with spontaneous myxedema.[2]

The reports on the hypophysis in cases of endemic cretinism are no less conflicting. Older publications in the European literature mention normal size of the hypophysis or diminution of size, especially of the anterior lobe, or enlargement of the organ, up to 1.55 gm. Histologically, atrophy of the cell cords in the anterior lobe, scanty chromophilic cells, fibrosis, increase of colloid, etc. have been described. Some authors saw proliferation of the chromophilic cells; others describe the hypophysis as without any change. The largest amount of material of endemic goiter was examined by Brauchli (19) in Switzerland. In the majority of the glands in Bern the chief cells were found increased in number and in about one-half of the cases the eosinophilic cells as well. According to Wegelin (9) (Switzerland) in higher degrees of endemic cretinism the hypophysis is usually enlarged, the sella turcica wide and deep and the chief cells proliferated. In older people the hypophysis may show pyknosis or balloon-like inflation of the nuclei as well as calcium concretions scattered through the anterior lobe. In one case Kraus and Holzer (20) saw enlargement of the hypophysis, many old and recent foci of colloid liquefaction in the anterior lobe and pars intermedia, and in another case proliferation of cells similar to Kraus' transitional cells together with a small colloid cyst in the anterior lobe and rather numerous calcified epithelial cells. Enlargement and increase in weight of the hypophysis up to twice the normal value with hyperplasia of either the chromophilic or chief cells may be seen in cases of atrophy of the thyroid gland, of congenital goiter and colloid goiter even without signs of hypothyrosis. In some cases of nodular goiter the hypophysis was found decreased in size and weight.

The cause of the very different behavior of the hypophysis in the various pathological thyroid conditions is not known. The nature of the thyroid disease, its degree and duration, as well as the age and sex of the individual involved, and last the presence or absence of an endemic character of the thyroid disease may play a part.

As for the cause of the change in the hypophysis in thyroid deficiency, Berblinger (14) thought of substances foreign to blood plasma which in hypothyroid states enter the blood and produce hyperplasia of the chief cells and enlargement of the hypophysis in analogy with placental and fetal extracts and peptone, which administered intravenously to animals, cause similar changes in the hypophysis.

THE HYPOPHYSIS IN MALIGNANT BLASTOMAS

From the investigations of Karlefors (21) as well as Berblinger and Muth (22) it is evident that malignant tumors, both carcinoma and

[1] A review of the pertinent literature is found in this paper.

[2] This paper contains a comprehensive review of the pertinent literature.

sarcoma, but especially the former, cause hyperplastic changes in the anterior lobe of the hypophysis. According to these authors the chief cells in about 50 per cent of the cases appear increased in number. Kraus (23) examined 7 cases of carcinoma of the genitals in females, some of whom had excreted prolan in the urine, and found the average weight of the hypophysis increased to 0.85 gm. This was associated with proliferation of not only the chromophobe but also the chromophil cells, especially the eosinophils. No regularity of the cell types participating in the proliferation was found. While Wohlwill (24) was unable to confirm a constant shift in the quantitative relation of cells of the anterior lobe in cancer-stricken individuals, Wyeth (25) found the chromophils especially proliferated in these glands, the average weight of which was increased in both sexes and in all age classes. The histological examination of the hypophysis in women with breast carcinoma does not reveal, according to Steiner and Dunham (26), important differences in the percentage of chromophobes, acidophils or basophils compared with those in women with tumors of other types.

In cases of sarcoma and melanoblastoma, the hypophysis may be remarkably enlarged and show abundant eosinophilic cells. The dependence of the cytological picture in the anterior lobe upon various factors, such as age, state of the gonads, obesity, contracted kidneys, hypertension, etc., makes it conceivable that, in cases of carcinoma or sarcoma, these factors may influence the changes produced by the malignant tumor.

According to Kutcherenko (27), the colloid secretion in the hypophysis in malignant tumors is more abundant than normal and, according to Wohlwill (24), circumscribed fibrosis in the anterior lobe is frequent.

With regard to the frequent elimination of gonadotrophins by patients with malignant tumors, some investigators believe that the malignant blastoma stimulates the anterior lobe to increased production of follicle-ripening hormone which is then stored in the tumor itself. The hyperplastic changes in the anterior lobe would be the morphological expression of the increased activity.

Significant are the enlargement and the cellular changes of the anterior lobe in cases of chorionepithelioma in women as well as in men. The histological picture of the anterior lobe shows the chief cell converted into cells typical of pregnancy cells (Novak and Koff, 28; and others). In cases of chorionepithelioma of the testis in which there are gynecomastia, secretion of colostrum and elimination of follicle-stimulating and luteinizing hormones, the hypophysis has been found enlarged with the chief cells hypertrophic or transformed into cells very similar to pregnancy cells (Mathias, 29; Herlant, 30; etc.). Entwisle and Hepp (31) also mention an increase of basophilic cells, along with a decrease in the number of eosinophilic cells.

THE HYPOPHYSIS IN LONG-CONTINUED INCREASED INTRACRANIAL PRESSURE

Long-lasting increase of the intracranial pressure due to various space-occupying processes causes enlargement of the hypophysis provided that the communication between hypophysis and brain has not been interrupted (Kraus, 32–34). This enlargement, to which females are more inclined than males, is due to hyperplasia of the parenchyma, in which all three cell types of the anterior lobe may participate. The chief cells, in particular, offer a characteristic picture since they are enlarged and abundantly proliferated and sometimes form large strands. This occurs mainly in the lateral parts of the anterior lobe close to the posterior lobe. The proliferated eosinophilic cells are usually smaller and form ill-defined foci beside the normal eosinophilic cells. The basophilic cells may proliferate in large areas containing mature basophilic cells as well as their non-granulated precursors, the so-called transitional cells. Adenomatous hyperplasias or even small adenomas also are seen in these glands occasionally.

The conditions under which space-occupying intracranial processes cause hyperplasia of the hypophysis are long-lasting pressure of considerable degree and uninterrupted connection of the hypophysis with the interbrain. Interruption of the connection leads inevitably to atrophy of the anterior lobe (Kraus, 33).

The intracranial lesions causing hyperplastic changes in the anterior lobe are primary blastomas of the brain and of the meninges and chronic hydrocephalus. Hyperplastic changes

in the hypophysis are usually not observed in cases of brain abscess and metastatic brain tumor. The reason for this might be the lower degree of pressure exerted by the brain abscess and the shorter duration of the intracranial pressure in metastatic brain tumors.

The hyperplastic changes of the hypophysis described are found in about 80 per cent of the cases. Females, as a rule, show higher values, perhaps because of the greater normal weight of the female hypophysis. According to Kraus' investigation, based on material of 125 cases, the average weight of the hypophysis in males with increased brain pressure was 0.79 gm. as compared with the normal weight of 0.63 gm., and in females it was 0.86 gm. as compared with 0.71 gm. for the normal.[3]

The cause of the hyperplastic changes in the anterior lobe produced by long-lasting intracranial pressure is not known. They might express increased activity of the anterior lobe, perhaps compensatory in nature and caused by functional insufficiency of the hard pressed vegetative centers in the interbrain.

Anterior-lobe changes in chronic elevation of brain pressure, according to Kraus (36), are accompanied in more than 80 per cent of the cases by a cystic degeneration of the ovaries and that not only in mature females but also in children. This has been interpreted by Kraus as a gonadotropic hyperpituitarism as suggested by the hyperplasia of the hypophysis. This assumption is supported by the facts that patients with increased intracranial pressure often eliminate gonadotrophin in the urine and that the ovaries of juvenile mice respond to the administration of that hormone with a condition that has the greatest resemblance to the cystic degeneration of the human ovary.

Another finding in chronic brain pressure caused Kraus (37) to believe that the hyperplastic hypophysis also produces an increased amount of corticotropic hormone. He found in 89 per cent of all cases with increased intracranial pressure hyperplasia of the adrenal cortex and in 85 per cent the hyperplastic changes of the adrenal cortex coincided with those in the anterior lobe. While the normal weight of the adrenals in adults varies from 7 to 10 gm., the average weight for both glands in Kraus' cases was 13.5 gm.

Central fatty infiltration of the liver found in 80 per cent of his cases with chronic elevation of the brain pressure was interpreted by Kraus (38) as possibly another manifestation of hyperpituitarism, since administration of anterior-lobe extract may produce in experimental animals fatty infiltration of the liver.

In almost all of these cases no other condition could be disclosed which would have explained the described changes in ovaries, adrenals and liver except the intracranial lesion with the secondary involvement of the hypophysis.

THE HYPOPHYSIS IN HYPERTENSIVE STATES, CONSTITUTIONAL OBESITY, AND SOME OTHER CONDITIONS

The first author who noticed increase of basophilic cells in the hypophysis in hypertensive cases was Berblinger (39, 40). He found it most frequently in uremia with 87.5 per cent of the cases and second to this in malignant nephrosclerosis with 83.3 per cent. In benign nephrosclerosis the proportion was 76.2 per cent and in chronic glomerulonephritis, including the state of contraction, only 61.5 per cent.

According to Kraus and Traube (41), 56.2 per cent of persons with essential hypertension show on increase of basophilic cells, while in hypertensive cases with contracted kidneys results similar to those of Berblinger are obtained. However, not only in hypertensive cases did Kraus see the basophilic cells increased but also in individuals with so-called "constitutional" obesity. Here the proportion of positive cases was 81.8 per cent of all examined. Because hypertension, vascular nephrosclerosis, and obesity are encountered frequently in hypersthenic individuals—certainly much more often than in asthenic or normosthenic ones—Kraus (42) examined the hypophysis of healthy men belonging to the hypersthenic or athletic type and in those also found the basophilic cells increased—a finding later corroborated by Rasmussen (40).

Since in persons with essential hypertension, vascular and inflammatory contracted kidneys (as well as in obese and hypersthenic persons) the adrenal weight generally is increased, it is

[3] Herlant (35), using rats for his experiments observed an increase of basophilic cells and increased colloid excretion after raising the intracranial pressure by ligature of the jugular veins or by intracerebral injection of hypertonic salt solutions.

not surprising that Kraus (42), on examination of the hypophysis in cases with hyperplastic adrenals, found an increase of basophilic cells in not less than 75 per cent of the cases. Based on these findings and, in particular, on his discovery that the basophilic cells undergo excessive destruction in Addison's disease (just as they are usually decreased in number in asthenic individuals with tuberculosis and juvenile diabetes) Kraus came to the conclusion that the basophilic cells represent a part of the mechanism controlling blood pressure.

In view of the significance of the blood cholesterol in hypertension, it might be of interest to note that there is a remarkable correlation between the titre of that substance and the number of basophilic cells in the hypophysis. The cholesterol content of the blood is higher in hypersthenic than in asthenic persons. Indeed, the investigations of Kraus (43) show that in hypersthenic individuals there is a tendency to an increase, and in asthenic persons to a decrease, of basophilic cells in the hypophysis. The relation between the hypophysis and cholesterol metabolism also was emphasized by Moehlig and Bates (44) some years ago. In hypersthenic persons suffering from one of the diseases to which this type is prone, such as obesity, hypertension, arteriosclerosis, gout, etc., the cholesterol content of the blood, according to Mjassinkov (45), appears increased above the average level of this constitutional type. And, like the cholesterol content in the blood, the basophilic cells in the hypophysis show increase in these conditions.

Regularity in the relative content of basophilic cells in the two lobes in hypertensive and other cases does not exist, though it is evident that, in cases with a great many basophilic cells in the anterior lobe, a strong basophilic invasion of the posterior lobe is much more frequent than in cases with fewer basophilic cells in the anterior lobe. This has been confirmed by Hawking (46), in whose opinion the different behavior of the basophilic cells in the two lobes supports the idea (expressed by Kraus and by Rasmussen) that there must be a functional difference between these two cell types. Rasmussen pointed also to the morphological difference between them. There is a slight difference in the color of the basophils of the two lobes; the basophils of the posterior lobe do not attain the size of those in the anterior lobe nor are they vacuolated. Kraus emphasized the quite different local conditions under which the basophilic cells of the two lobes act, for those in the anterior lobe are in closest contact with thin-walled capillaries, apparently emptying their products immediately into the blood stream; in contrast, the basophils in the posterior lobe appear embedded in neuroglia where they are to be converted partially into pigment and partially into hyaline bodies—a process that has not yet been clarified as to its physiological significance. (For more information see Rasmussen, 47).

The problem of the so-called basophilic invasion of the posterior lobe and its relation to hypertension has been investigated and discussed by many authors, especially in recent years (Leary and Zimmerman, 48). While Kraus regards the increase of the basophilic cells seen in such a great percentage of hypertensive cases of different types as a secondary phenomenon (perhaps as the expression of a special functional adaption), some authors are inclined to attribute pathogenetic significance to the "basophilism" of the hypophysis in general or to the basophilic invasion of the posterior lobe in particular. Impressed by the experiments of Anselmino and Hoffman and by the fact that 6 of 9 hypophyses of cases with eclampsia and with essential hypertension showed a heavy infiltration of basophilic cells into the posterior lobe, Cushing (49) came to the following conclusions: the source of the hypertensive disorders lies in the posterior lobe and the extent of the basophilic invasion is a measure of the posterior lobe activity. In eclampsia and essential hypertension in young people, the excessive infiltration of basophilic cells into the posterior lobe represents the histological basis of these two conditions. It may also possibly be related etiologically to the atherosclerosis of old age.

Other authors as Rasmussen (this author basing his conclusion on differential cell counting), Hawking (46), Butt and Van Wart (50), Parsons (51), Spark (52), etc. deny or question the rôle of the basophilic hyperplasia as an etiological factor in hypertension. Cushing's viewpoint about the importance of the basophilic invasions of the posterior lobe in eclampsia was opposed by Kraus (53) in whose opinion

the former has no etiological rôle in that condition. According to Kraus, the "basophilism" of the hypophysis, including the posterior lobe, in cases of eclampsia is a secondary phenomenon attributable to the hypertension, to the kidney disease, and to the frequently present obesity. In Europe at least 75 per cent of all eclamptic women belong to the obese type. Besides, it should be mentioned that basophilic hyperplasia is not a constant finding in eclampsia, just as it is not in other hypertensive conditions nor in obesity. This fact is more compatible with the supposition that the increase of basophilic cells in all these conditions is a secondary phenomenon rather than the primary cause.

To reiterate, though all investigators agree that the basophilic cells of the hypophysis are increased in the majority of hypertensive cases, most of them do not believe in the etiological significance of this finding. Rather the "basophilism" in hypertensive cases might be a compensatory measure on the part of the basophilic cells, which seem to represent a part of the mechanism controlling the blood pressure.

Increase in the number of basophilic cells may be encountered in many cases of syphilitic mesaortitis and paresis; however, in the latter not only the basophils but also transitional cells (the precursors of the basophils) are often increased (Kraus, 54). The hypersthenic habitus and the obesity in many of these cases might be accountable for the increase of basophilic cells rather than the disease itself. In liver cirrhosis, the basophils sometimes are increased in number at the expense of the eosinophils, but they are supposedly always absent in the posterior lobe (Barrelet, 55).

The findings in the hypophysis in dementia precox are not uniform. Dercum and Ellis (56), Mott and Robertson (57), and Morse (58) saw proliferation of connective tissue in addition to the increase of chromophilic cells, emphasized especially by Dercum and Ellis (see bibliography of Munzer and Pollak, 59).

Benda (60, 61) studied the hypophysis in mongolism and found an increase of eosinophilic cells, while in 10 other cases the chromophobic cells were predominant. Only in 4 cases were the basophilic cells hyperplastic, these being similar to castration cells. Benda sees an indication of a functional disorder in these changes, though they have no etiological significance. The increase in the basophilic cells of the hypophysis recently described by Gray (62) in a case of functioning islet-cell carcinoma in an obese 48-year-old woman might be due to the obesity rather than to the hyperfunction of islet tissue.

Spark (52) observed hyperplasia of both chromphilic cell types in 4 individuals who were treated with a considerable amount of estrogenic hormone, thus duplicating the finding seen in animals after administration of large amounts of female sex hormone.

HYPERPLASTIC CHANGES OF THE HYPOPHYSIS IN CUSHING'S DISEASE AND SOME RARE TYPES OF OBESITY

As far as Cushing's disease is concerned, hyperplastic changes of the basophilic cells have been observed in only few cases, as for instance, in a case of Rutishauser (63), in which numerous small foci of newly formed basophils, rather regularly scattered through the anterior lobe, were found. Against that the overwhelming majority of cases show a basophilic adenoma and in a minority of cases no proliferation of basophils whatever has been encountered.

In the syndromes to be discussed in the following paragraphs hyperplastic changes of the hypophysis seem to be a rather constant finding. These conditions are the syndrome of Morgagni-Stewart-Morel, the cerebral hyperglobulia, Dercum's adiposis dolorosa and the syndrome of Bardet-Laurence-Moon.

Only scanty and rather conflicting reports on the hypophysis in the syndrome of Morgagni-Stewart-Morel are found in the literature. This syndrome, which chiefly involves females, is characterized by obesity, amenorrhea, virilism, headaches, weakness, mental changes, visual disturbances, polyphagia, polydipsia, polyuria and hyperostosis of the skull, either diffuse or more often limited to the frontal squamma and known as hyperostosis frontalis interna (Stewart, 64; Morel, 65; Henschen, 66; Ritter, 67; Rossier and Secretan, 68; Knies and LeFever, 69; and others). The fact that in some of these cases acromegalic changes have been observed early called attention to the hypophysis. Stewart and later Henschen in particular have proposed a hypophysial origin of the syndrome.

Henschen found an adenomatous hyperplasia of the anterior lobe made up of eosinophilic as well as basophilic cells and furthermore reduction of the chief cells and basophilic invasion in the posterior lobe. According to Morel, either hypertrophy or tumors of the hypophysis, with damage to the infundibular region and the third ventricle are found in the hypophyseodiencephalic system. Many changes described might be only of senile or incidental nature, as pointed out by Knies and LeFever. In a case of Kraus (reported by Ritter) concerning a women 37 years of age with extreme obesity, atrophy of the ovaries and marked hyperostosis frontalis interna, the following changes were revealed. The hypophysis was enlarged (0.8 gm.) and distinguished by a remarkable increase of basophilic cells in the anterior lobe and a moderate invasion of the posterior lobe, but the eosinophils and chief cells were not altered. There was a slight diffuse colloid goiter. The adrenals weighed 16 gm. (compared with 7–10 gm. as the normal value) and showed a hypertrophic cortex, very rich in lipoid. The ovaries were shrunken, with marked paucity of follicles. The diencephalon was histologically normal. A greater number of reliable postmortem reports are necessary before the rôle of the hypophysis in the pathogenesis of Morgagni's syndrome can be clarified.

Basophilic hyperplasia of the hypophysis and hyperplasia of the adrenal cortex were described by Kraus in 2 cases of cerebral hyperglobulia, a syndrome characterized by obesity, hyposexuality, narcolepsy and polycythemia. One of these reports, published by Ritter (67), concerned a male 50 years of age, 256 lbs. in weight and with a red cell count of 7,290,000. He was impotent for about 9 years; his narcolepsy was manifested by the fact that he fell asleep at any time and in any position if not kept busy. The hypophysis weighed 1 gm. (compared with the normal value of 0.63 gm.) and exhibited an excessive proliferation of basophilic cells in the anterior lobe with no invasion of the posterior lobe. In addition to that there was an adenomatous colloid goiter, lipomatosis of the parathyroid glands and marked lipoid hyperplasia of the adrenals (20 gm.). A thorough histological examination of the interbrain demonstrated no pathology.

The changes found in the hypophysis and adrenals are not the cause of the syndrome but they represent a part of the disturbance in the fat metabolism, which leads to the obesity. The same changes, as mentioned before, can also be found in other types of obesity, such as constitutional obesity, Cushing's disease, Morgagni's syndrome, etc. The polycythemia might have a causal connection with the changes in hypophysis and adrenal cortex, since this sign is often associated with tumors of those structures (Guillain, Lechelle and Garcin, 70; Moehlig and Bates, 44; etc.). Polycythemia is not a rare finding in Cushing's disease, and several times has been seen associated with interrenalism (hyperadrenocorticism). The significance of the hypophysial, as well as adrenal, function in the production of erythrocytes has been proved by animal experiments performed by Houssay and associates (71), Bazett (72), Moehlig and Bates, etc.

There are numerous reports on findings in the hypophysis in Dercum's disease or adiposis dolorosa. They differ considerably and are mostly not very accurate. Some writers mention hyperplastic changes of the anterior lobe; but more frequently tumors are reported. The disease, chiefly involving women, is characterized by huge, more or less circumscribed masses of subcutaneous fat tissue, which are very painful. In addition to the painful obesity, asthenia, fatigability, epileptiform seizures and mental disturbances, bullae or ulcers on the extremities can be observed. Dercum and McCarthy (73) found an adenocarcinoma of the hypophysis and an enlargement of the right adrenal; Burr (74), a walnut-sized glioma of the hypophysis; Guillain and Alquier (75), a considerable enlargement of the hypophysis with increased fibrous tissue; Foot, Good and Menard (76) described an adenomatous hyperplasia besides sclerosis of the hypophysis and bilateral suprarenal adenomas; and Winkelman and Eckel (77) saw an adenoma of the hypophysis with enlargement of the sella turcica and adenomatous hyperplasia of the adrenal cortex. No statement is made concerning the type of cells of which the hypophysial new growths (adenoma or hyperplasia) were composed. Yet it seems to be sure that the adenomatous or hyperplastic changes in the hypophysis and in the adrenal cortex are essential

in the pathogenesis of Dercum's disease, just as they are in other syndromes with the obesity as a constant and integral symptom.

Obesity and genital dystrophy are the two cardinal symptoms of Bardet-Laurence-Moon's syndrome, which in addition is distinguished by retinitis pigmentosa and a number of congenital anomalies, the most frequent being polydactylism and syndactylism. Other symptoms of the disease, which shows familial occurrence, may be mental deficiency, bilateral cataract, skull deformities, genu valgum, in some cases atresia ani, etc.

Until 1936 apparently no autopsy findings were known. Then Bogaert and Borremans (78) reported the first autopsy which revealed a slight enlargement of the sella turcica together with a small area devoid of nuclei within the hypophysial stalk, indicating apparently a circumscribed necrosis. In a case of Loepp (79), the sella was enlarged and contained a cyst with epithelial rests in its wall (quoted by Anderson, 80). In two reliably examined cases —one published by Griffiths (81) and the other by Anderson—there was a strikingly high proportion of basophilic cells and relative paucity of eosinophilic elements. The case of Anderson was complicated by bilateral hydronephrosis and hypertension. The increase in the number of basophilic cells in these cases is to be evaluated like that in the aforementioned types of obesity and does not represent a specific lesion. One should also remember the fact that a high percentage of hypertensive conditions are associated with an increase of basophilic cells in the hypophysis.

Various lesions of the brain were found in Bardet-Laurence-Moon syndrome, and the theory was advanced by some authors that the syndrome represents a cerebral form of adiposogenital dystrophy. The fact that the syndrome is familial and displays so many malformations as regular findings indicates that genetic factors play a decisive rôle in its pathogenesis and that it is not to be considered merely as an endocrine disorder.

All these types of obesity, discussed in this chapter, show a partial resemblance because of certain common features, such as the disturbance in fat metabolism, the hypogenitalism, the proliferation of the basophilic cells in the hypophysis and the hyperplastic changes of the adrenals. This fact best illustrates the importance of these two endocrine organs in the sexual sphere as well as in fat metabolism and in their disorders.

REGENERATIVE HYPERPLASIA

The regenerative power of the hypophysial parenchyma seems to be slight as is evident from the fact that cicatrizing lesions, such as result from infarcts for instance are not accompanied by any noticeable new formation of parenchyma. The writer saw in a case of Addison's disease, in which the basophilic cells as a rule are markedly diminished in number, multiple foci made up of newly formed chief cells, transitional cells, and slightly granulated (evidently young) basophils. He interpreted these cell foci as regenerative in nature, particularly because they were found in areas depleted of parenchyma and partially sclerotic. Berblinger described and pictured a hypophysis with an apparently compensatory regeneration and hypertrophy of eosinophilic cells secondary to destruction of parenchyma by cysticercosis (hypophysitis cysticercosa). The very sparse statements concerning regenerative processes in the anterior lobe illustrate best the negligible regenerative power of the glandular part of the hypophysis, despite its remarkable tendency to hypertrophy and hyperplasia. It must, of course, be admitted that it may sometimes be difficult to recognize a moderate degree of regeneration. Lack of lipoid is one of the criteria to help differentiate between old and newly formed parenchyma, the latter being characterized by almost complete absence of lipoid.

SUMMARY

A review is offered of the morphological findings in the hypophysis in a variety of conditions, such as: castration, thyroid disorders, malignant blastomas, long-continued intracranial pressure, hypertensive states, certain constitutional disorders, Cushing's disease and certain rare obesities. The changes found in these conditions are chiefly hyperplastic in nature and involve one or two or all three cell types of the anterior lobe. Regenerative hypophysial hyperplasia is also briefly considered.

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EDITORIAL

THE CONTROL OF PITUITARY SECRETION

MANY researches—and especially those of the past two decades—have proved beyond question that the anterior pituitary gland has important regulatory influences on various other endocrine structures. The evidence of pituitary control is most adequate in case of the thyroid, the adrenals and the gonads, but probably the parathyroid glands also are under a similar influence. Obviously through these subsidiary agencies the secretions of the anterior pituitary gland exert far-reaching effects on the metabolic processes of the body. In view of the fact that clinical symptoms are largely determined by metabolic changes, these influences are no doubt of importance in general pathology as well as in the endocrine disorders, proper.

The problem, "what regulates the regulator," is thus one of signal importance in experimental as well as practical clinical situations. The best known of the pituitary regulators are the hormones of the regulated glands themselves. Thus, for example, an excess of gonadal secretion causes, directly or indirectly, a depression of the pituitary gonadotropin output; contrariwise, a deficit of gonadal hormone leads to an excess of circulating gonadotropin.

For several years, thanks to the efforts of Drury, Brook and others, there has been available evidence that copper salts can cause a discharge of gonadotropin. Fevold and collaborators have noted that yeast extracts exert a similar influence which has been assumed to be due to copper contained in the extract. In these columns attention has been called also to a report published by Fugo and Gross in 1942 to the effect that the drug yohimbine has a specific stimulating effect on the anterior pituitary leading to prolonged estrus as well as corpus-luteum formation in intraocular implants of immature ovaries.

A further study of influences that affect the anterior pituitary has recently been published by Bradbury[1] from the Federal Bureau of Dairy Industry at Beltsville, Maryland. Carrying forward previous work of Friedman and collaborators, Bradbury has confirmed the presence of a substance in green plants that, when given parenterally, induces ovulation. In the more recent studies the green-plant material from such a variety of sources as alfalfa, oats, corn, carrot tops and lawn clippings has been found to contain the ovulating factor. This study of Bradbury's was made principally with an extract of oats prepared from frozen juice and kept in a dry form until used. In the tests post-partum or isolated post-pseudopregnant female rabbits were used. The condition of estrus was judged by abdominal palpitation of the uterus, and the condition of the ovaries and uteri was determined by laparatomy. At autopsy the anterior pituitary glands were removed and assayed for gonadotropin activity. The plant extract was given intravenously but, because of toxic qualities of some preparations, had to be used in restricted amounts. There was found to be a seasonal variation in sensitivity of the test-animals; those used in the fall and winter months were less responsive. Pre-treatment with estrogen or copper acetate increased the responsivity.

In brief, the results of the study indicated that the plant-juice extracts when given singly or combined with pituitary extracts caused ovulation in the adult rabbit, but not in the infantile rat. The pituitaries of the injected rabbits afforded evidence that a discharge of gonadotropin had taken place in that they contained less than the normal quantity of ovary-stimulating hormone. The plant-extract factor was therefore not itself a gonadotropin but a pituitary-stimulating factor.

Whether this study will have any immediate clinical application remains for future research to determine. The use of crude juice extracts themselves is contraindicated by their toxic quality. It would seem possible, however, that by suitable fractionation a non-toxic pituitary-stimulating factor might be derived. In any case the research is of value in affording further evidence that in animals, or in man, the secretion of pituitary-regulating factors may actually be influenced by agents other than the recognized hormones. By so much is hope stimulated that ways may be found by control of diet or otherwise to regulate the pituitary regulator. *R.G.H.*

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LETTER

THE BITTERLING TEST

To the Editor:

In your recent editorial on "Rapid Tests for Pregnancy" you mention that the female bitterling test of Fleischmann and Kann proved non-specific for pregnancy. We would like to point out that the lengthening of the ovipositor of the female bitterling (*Rhodeus amarus*) due to estrogen was never suggested by us as a possible test for pregnancy. We were the first to report this reaction (*Arch. f. d. ges. Physiol.* 230: 662. 1932) as a result of studies on the comparative physiology of sex hormones. We used it to demonstrate the possibility of influencing cyclic changes in the sex organs of fishes with the same compounds which influence analogous changes in higher vertebrates. This reaction was then proposed by Kanter, Bauer and Klawans (*J. Am. Med. Assn.* 103: 2026. 1934) as a pregnancy test. After this paper had come to our notice we again emphasized (*Klin. Wochnschr.* 14: 644. 1935) that we were concerned only with the biologic aspects of the test and that it was for the obstetrician to decide whether it could be put to any practical use. At first we held the test specific for estrogens, but further work by Kleiner, Weisman and Mishkind (*J. Am. Med. Assn.* 106: 1643. 1936; *Science* 86: 160. 1937), Duyvene de Wit (*Endocrinol.* 24: 580. 1939) and by Fleischmann and Kann (*Science* 87: 305. 1938) showed that a large number of steroids could stimulate the growth of the ovipositor in female bitterlings.

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ASSOCIATION NOTICES

ANNUAL MEETING CANCELLED

In compliance with request of Director of War Mobilization and Reconversion, James F. Byrnes, your Council was polled and voted (1) to cancel the 1945 annual meeting of the Association, (2) to continue the terms of the present officers for another year, and (3) that the Ciba and Squibb Awards be made in 1945.

CARL R. MOORE, *President*
HENRY H. TURNER, *Secretary-Treasurer*

ENDOCRINE MONOGRAPHS

The Council of the Association for the Study of Internal Secretions has authorized the publication of a series of Endocrine Monographs. These monographs will provide for the publication and distribution of the results of experimental or clinical investigations which are too extensive in scope and form to be published in the Journals. The proposed series of monographs will also provide a means of publication for highly technical and detailed reports of experimental or clinical endocrinology which could not be published and distributed profitably by other publishers. Extensive and detailed reviews, summaries of investigations and critical analyses of progress in fields of laboratory or clinical investigation will also be considered appropriate for monographic publication.

Manuscripts are desired which with text, tables, and illustrations will appear in a book of 150 or more pages. These monographs will be issued only as material warrants. The successive volumes will appear in a uniform format and will be published and sold by the Association.

Investigators who wish to contribute extensive material from the field of their special interests are invited to communicate with one of the members of the Editorial Committee.

E. L. SEVRINGHAUS
W. O. THOMPSON
E. T. ENGLE, *Chairman*
Editorial Committee

NOMINATIONS FOR AWARDS OF THE ASSOCIATION

Two Awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. The work may be either clinical or in the basic sciences. A special Committee of five members of the Association chooses the recipients of these Awards, subject to ratification by the Council.

Each member of the Association has the privilege of making one nomination for each Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions in endocrinology and by a bibliography of his most important papers with reprints if possible. Five copies should be sent to the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, *not later than March 15, 1945*. The Awards are described below.

The E. R. Squibb and Sons Award

The E. R. Squibb and Sons Award of $1,000.00 was established in 1939. It was given in 1940 to Dr. George W. Corner, in 1941 to Dr. Philip E. Smith, in 1942 to Dr. Fred C. Koch, and in 1944 to Dr. Edward A. Doisy. No age or other special limitation is stipulated by the Donor of the Award. So far it has been given for long-continued work of a high quality.

The Ciba Award

The Ciba Award was established in 1942 and is to be given to an investigator not over 35 years of age. No recipient was selected in 1942. In 1944 the Award was given to Dr. E. B. Astwood. The Award is for $1,200.00. If the recipient chooses to use the Award to aid in working in a laboratory other than the one in which he normally is located, the Award will be increased to $1,800.00

CARL R. MOORE, President
HENRY H. TURNER, Secretary

Abstracts of

CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. *Collaborators:* F. A. DE LA BALZE, ISRAEL BRAM, RUCKER CLEVELAND, JOHN W. EVERETT, ANNE FORBES, E. C. HAMBLEN, CHARLES W. HOOKER, R. G. HOSKINS, JANET W. MCARTHUR, THOMAS H. MCGAVACK, J. R. REFORZO MEMBRIVES, A. E. MEYER, DORIS PHELPS, E. C. REIFENSTEIN, JR., RUTH ST. JOHN, HAROLD WOOSTER, AND J. ZANARTU.

BOOK REVIEWS

GOLDZIEHER, MAX A.

The Adrenal Glands in Health and Disease. F. A. Davis Company, Philadelphia, 1944.

The author brings to bear what is probably the longest and broadest personal experience of anyone who is now writing on the adrenal glands. His earlier work was that of a Continental, centering in the field of morphologic pathology. Later, he turned to clinical medicine but continued his laboratory interests, his subsequent experimental studies being more along physiological lines. He began publishing on the adrenals at book length a third of a century ago.

The current book in considerable degree mirrors the author's somewhat unusual background. For example, he has long maintained a closer contact with the Continental literature than have most Americans and his writings are correspondingly more influenced by that literature. As to his physiological researches, it would seem in retrospect that he rates priority as the first to have derived significantly potent adrenal-cortex extracts, credit for which success has been considerably delayed, possibly because of the author's not having published in media—and in terms of experiences—best known to physiologists.

The author is perhaps somewhat unconsciously biased in his selections of laboratory data, being inclined to brush off such as do not fit in well with his clinical experience, on the grounds that a rat is not a man. It remains true, however, that physiological principles are principles irrespective of species and, by and large, those demonstrated in rats are more readily accepted than those which seem to be apparent in man precisely because a rat is a rat and lends itself much better than does a man to rigid experimental control. But the converse is, of course, equally true, namely that no physiologist is able to reproduce many of the enlightening experiments that nature sets up in the human species. In consequence of these respective characteristics both clinicians and physiologists are tempted to an occasional *non sequitur*.

Throughout the book the author tends, in the reviewer's opinion, to confuse adrenalin pharmacology with adrenalin physiology. Irrespective of experimental or expository ingenuity the fact remains that before one can ascribe any clinical manifestation to excessive adrenalin discharge it is antecedently necessary to show that the body is reacting throughout the sympathetic domain. For example "adrenalinogenic hypertension" can be such only when accompanied by dilated pupils, sluggish gastro-intestinal functions, elevated blood sugar and what not. In the current publication the author has made some increased utilization—but not enough—of the fact that the adrenal cortex shares in various of the functional attributes of the medulla of the gland. For example, the cortex is a much safer place to look for clinically significant pressor influences than is the medulla.

In its clinical aspects the book reveals broad experience and acumen and, on morphologic topics—physiologic or pathologic—it is often masterful. The work is divided into four chief sections: morphology, physiology, diseases, and pathophysiology. The discussion of adrenal extracts is excellent and up to date as is that of the metabolic relationships of the cortex. An especially satisfactory chapter is that dealing with the responses of the adrenal cortex to various agents and conditions. Two chapters on the pharmacology and toxicology of adrenal derivatives are notable for their scope and inclusiveness; the only omission that impressed the reviewer is the rather extensive studies that have been made on the effects of adrenalin on the distribution of the blood and especially the vasodilator effect of that hormone in skeletal muscles. Stress is laid on the significance of the fetal adrenals as affording a mechanism for adapting the growing organism to the low oxygen tension of the fetal blood. To the adrenals also is ascribed importance in the control of post-partum water

exchange. Evidence is cited that adrenal failure is an important factor in toxemia of pregnancy and excellent results are reported in the use of cortical extracts in the treatment of vomiting of pregnancy. The adrenals are also discussed in relation to ageing, nutrition, vitamine metabolism, low-oxygen environments, hypertension, cardio-vascular disorders, allergy, cancer, etc. The section on obesity is especially noteworthy. But the author does less than justice to Cannon's "emergency function" of the adrenals.

Conservative clinicians may question in some instances the author's statements regarding therapeutic values of endocrine preparations in that evidence of adequate control is not recorded. In view of the growing awareness of the potency of suggestion which, by allaying the patient's anxiety, may bring about significant changes even at the physiologic level, the physician will be increasingly constrained to show that he has not been misled by the *post hoc* fallacy in ascribing curative virtues to hormone preparations.

The foregoing criticisms should not be allowed to obscure the fact that the book is characterized primarily by many excellences. It is documented throughout by well-selected citations from the literature; admirable judgment is shown in quoting older as well as very recent publications. The style is flowing and often pungent. The illustrations are clear and well selected. On the whole the book can be recommended as the best-balanced and most adequate as well as up-to-date work on the adrenal glands that is now available in any language.—*R.G.H.*

HAMBLEN, E. C.

Facts for Childless Couples. Charles C Thomas, Springfield, Illinois, 1942, 1944.

The fact that this little book has reached a second printing attests to its appeal and its usefulness. As the title suggests, it affords a succinct discussion of the desirability of, and the technical procedures that are involved in, sterility studies. It emphasizes the fact that in a considerable proportion of the cases the infertility factors lie predominantly in the husband—a fact with which the laity are largely unacquainted. The author reaffirms the dictum that studies looking to improvement of fertility are inadvisable unless both would-be parents are investigated.

The first chapter deals with sociological, economic, ethical and practical aspects of infertility. The chapter makes over-all good sense but might perhaps have been couched in somewhat simpler terms. The following chapters deal with the male and female genital anatomy and physiology. Two succeeding chapters outline the technical procedures that are brought to bear in appraising reproductive efficiency. The next section deals with prognosis and treatment. The book closes with a final chapter on popular misconceptions. The author is notably less than enthusiastic regarding the practical possibilities of artificial insemination.

Excellent as the book is, it would lend itself rather easily to improvement. In numerous instances polysyllabic terms and somewhat unfamiliar concepts are used when simpler diction would have been adequate. On page 27 appears a cut which is over-detailed and especially overlabelled and which could profitably be considerably enlarged. Tucked into one corner of it is a magnified detail which is especially confusing. On page 32 on the other hand appears a cut that is notable for its clarity. When subsequent printings are required—as no doubt they will be—it is to be hoped that a glossary will be added. Altogether the book is one which can safely be put into the hands of the laity and should afford a time-saving resource for the busy practitioner.—*R.G.H.*

JAEGER, E. C.

A Source-Book of Biological Names and Terms, Charles C Thomas, Publisher, 1944.

Endocrinologists, even as other people, sometimes have occasion to coin new terms. Sometimes the neologisms are apt but often the hand of the amateur is evident in the final structure. Editors still have occasion to remodel the Greek-Latin mongrel, "polyglandular." Another recent item of interest is the discussion of the relative desirability of "trop" or "troph" in making up the names of the anterior-pituitary regulating hormones. Upon turning to Jaeger's book and using that item as a test case, it appears that the basic meaning of "troph" is "to feed" while that of "trop" is "to turn." Thus it would appear that recent proposals to reform "tropic" amount to retrogression from better to worse.

As to the book itself—perhaps no better characterization can be offered than that which appears on the jacket: "Greek, Latin, or other origins of the 12,000 elements listed are given and their concise meanings, along with numerous examples of their use in scientific nomenclature. If you wish to know the literal meaning of the words you use, this useful source gives the largest assemblage of such formative elements, or combining forms ever brought together in a single

volume. In scope it surpasses many times the most complete collections in unabridged dictionaries and scientific glossaries. It gives the key which unlocks the treasury of meaning of more than a million scientific names and terms."

To those who enjoy contemplating the natural history or architecture of words the book will offer delights.—*R.G.H.*

MEAKINS, J. C.

The Practice of Medicine. 4th Edition. C. V. Mosby Company, St. Louis, Missouri.

So well and so favorably known is this book that little more than the announcement of a new edition seems necessary. This edition differs from the preceding one mainly in two respects. Recognition is accorded to the growing importance of psychosomatic medicine; the importance of psychic factors in such disorders as backache, hypertension and anorexia nervosa is stressed. Such a list, incidentally, should also emphasize asthma, gastric ulcer and ulcerative colitis. As is true of medical text books in general, however, the orientation still remains essentially somatic with only passing acknowledgement of psychological components. What is especially needed now is a standard text book of medicine in which realistic account is taken of the fact that a majority of all symptoms that bring patients to doctors are only secondarily, if at all of somatic origin.

A second major modification from the third edition is the incorporation of the remarkable advances that have occurred in medicine in the past four years.

Of chief interest to the readers of this Journal are the chapters written by E. H. Mason on "Diseases of Metabolism" and "Diseases of the Ductless Glands," respectively. The two together occupy 143 pages. In general they are up-to-date and, for a section of that length, reasonably complete. In addition to numerous excellences of selection, balance, and style a few defects may be mentioned. First of all is the continued use of the hoary misnomer, "ductless glands." "Frölich's syndrome" is ascribed to anterior-lobe plus posterior-lobe pituitary deficiency rather than to the more important etiologic factor, hypothalamic dysfunction. "Thyroid extract" appears as a designation of desiccated thyroid substance. The section on the male gonads is notably incomplete, very little attention being paid to the numerous and recent important developments in that part of the field.

The book as a whole is well illustrated, some of the color plates being especially informing. The style is fluent and concise. It is well supplied with topical headings that give easy access to the contents. It is documented throughout with generally well selected bibliographies. Altogether it is a satisfying book that accomplishes admirably its purpose of fitting the needs of the busy practitioner who has not time to follow the wider-ranging writings of the specialists.—*R.G.H.*

SCHEINFELD, A.

Women and Men. Harcourt, Brace and Company, New York, 1943.

A sub-title for this book might be, "What sex means to mankind." Although written in the style and spirit of a reporter, the work is so well done as to deserve the attention not only of the laity but also of the scientifically sophisticated. The author in carrying out his task has drawn from the fields of sociology, anthropology, psychology, physiology, general biology and medicine. The book carries on in the general spirit of Havelock Ellis' *Man and Woman* but brings the subject up to date.

A fair estimate of the character of the book may be derived from some of the chapter headings: Myths and muddles, budding personalities, crossing the bridge, the two machines, sex life, division of labor, equality for women, pitfalls of the past, and marriage of tomorrow. One of the noteworthy features of the book is a series of very ingenious line drawings that both edify and instruct. The author has even succeeded in making lucid the complex phenomenology of chromosomal sex determination. In the book are set forth in charming and comprehensible style answers to a thousand and one questions that sometimes have the doctor nonplussed. The book closes with a comprehensive bibliography in which are cited many titles from diverse fields of learning—often interesting articles with which endocrinologists would not ordinarily be familiar.

This volume could be enthusiastically recommended for the doctor's waiting room table except for the fact that the replacement rate would doubtlessly be prohibitively high.—*R.G.H.*

SIMMONS, KATHARINE

The Brush Foundation Study of Child Growth and Development. II. Physical Growth and Development. National Research Council, Washington, 1944.

Those who are interested in norms of physical growth and development will find in this volume a wealth of well-analyzed material that was gathered from an unusually stable population.

The cross-sectional age-sex constants are given for 25 anthropometric dimensions.—*R.G.H.*

ADRENALS

INGLE, D. J.

The quantitative assay of adrenal cortical hormones by the muscle-work test in the adrenalectomized-nephrectomized rat. *Endocrinol.* 34: 191. 1944.

A method is described for the quantitative assay of adrenal cortical hormones by the muscle-work test using the adrenalectomized-nephrectomized rat. A unit of activity is defined as the work equivalent of a 0.2 mgm. dose of 17-hydroxy-11-dehydro-corticosterone administered twice during the test. A standard dosage-response curve was set up using 17-hydroxy-11-dehydrocorticosterone which permits the interpolation of work performance into units of the standard. The method is specific for the detection and estimation of biologic activity characteristic of the C_{11} oxygenated cortical steroids. Data illustrating the sensitivity and reliability of the test are presented.—*Author's Summary.*

MARTLAND, H. S.

Fulminating meningococcic infection with bilateral massive adrenal hemorrhage (the Waterhouse-Friderichsen syndrome). *Arch. Path.* 37: 147. 1944.

The series of 19 cases of the Waterhouse-Friderichsen syndrome analyzed in this report is perhaps the largest observed by one person, and the author's conclusions are based entirely on his personal experience. The Waterhouse-Friderichsen syndrome (cyanosis, purpura, petechias and bilateral massive hemorrhages in the adrenal glands without gross meningitis) is always that of fulminating, fatal meningococcemia, in which death occurs before there is notable invasion of the leptomeninges. This condition is not as rare as the literature suggests and is not limited to infants or children, but is apt to be encountered in adults whenever meningococcic infections are prevalent. The clinical and anatomic diagnosis is comparatively simple after attention has been called to the condition. The hemorrhages in the adrenal glands apparently are due to several factors: the toxins liberated by the enormous number of meningococci, the selective affinity of this toxin for capillary endothelium and the presence of a susceptible, rich, delicate capillary network in the adrenal cortex. However, death is due to the overwhelming meningococcemia rather than to acute insufficiency of the adrenal cortex. On account of the frequency of sudden and unexpected death, the sporadically occurring Waterhouse-Friderichsen syndrome in civilian life must sometimes be differentiated from food or chemical poisoning, trauma, negligence and even homicide.—*Abst. Arch. Neurol. & Psychiat.*

STEMMERMAN, MARGUERITE G. AND AUERBACH, O.

Adrenal amyloidosis. *Arch. Int. Med.* 74: 384. 1944.

This is a report on 468 cases of generalized amyloidosis in 449 of which examination of the adrenals was made. In all but 7 patients the underlying disease was tuberculosis. In 354 (81 per cent) of the patients the adrenals showed amyloidosis. Since amyloidosis produces extensive anatomic changes in the adrenal glands, not only by replacement of normal cortical tissue but by associated atrophy due to pressure, it is likely that some degree of adrenal insufficiency is produced, with or without evidence of frank Addison's disease. The authors reviewed the clinical and physiologic phenomena usually associated with adrenal amyloidosis in order to determine whether or not any criteria exist which may be helpful in determining to what extent these phenomena are due to adrenal insufficiency and to what extent to the underlying disease. Although no single criterion which can definitely settle this point was found, certain factors are useful. In the order of their relative importance and probability, the evidences of adrenal insufficiency are as follows: a positive or equivocal reaction to the salt restriction test in the absence of edema; low grade fever or normal temperature in the presence of active infection, and low blood pressure. Changes in renal function and carbohydrate metabolism, adynamia and gastrointestinal disturbances are of little or no assistance as differential criteria. Since a degree of adrenal cortical insufficiency probably exists in patients with severe amyloidosis and possibly some in those with moderate amyloidosis, an effort should be made to discover the severity of this insufficiency in every person with generalized amyloidosis. If evidence of even mild insufficiency exists, appropriate therapeutic measures should be instituted—*I.B.*

THOMAS, H. B., AND C. D. LEIPHART

Septicemia and purpura with adrenal hemorrhage in the adult (Waterhouse-Friderichsen

syndrome). A discussion of the rôle played by the adrenal gland in the production of the syndrome. *J.A.M.A.* 125: 884. 1944.

The picture described by the authors is one of fulminating sepsis complicated by widespread hemorrhage into the skin and other organs including the adrenals. The patients are usually infants and the organism when one is isolated is usually a meningococcus. The theory that rapid death in shock which is the usual outcome results from the adrenal hemorrhage is attacked on the following grounds: I. Typical cases have been reported in which the adrenals were found intact. 2. Collapse develops much more rapidly than it does following surgical removal of both adrenals (in dogs). 3. When recovery occurrs it takes place more rapidly than can be accounted for by the adrenal regeneration.—*A.P.F.*

THORNE, G. W.

Clinical use of extracts from the adrenal cortex and of synthetic products having similar action. *J.A.M.A.* 125: 10. 1944.

The author takes up only the treatment of adrenal cortical insufficiency feeling that the value of adrenal extract in non-specific conditions such as burns, infection and shock is still controversial. The diagnosis and management of adrenal insufficiency is discussed and the criteria for judging the adequacy of treatment laid down. Attention is called to the fact that adrenal extracts correct disturbances both in carbohydrate metabolism and electrolyte balance, whereas desoxycorticosterone, which is the only cheap pure adrenal steroid available, affects only the latter. Detailed directions for the treatment of chronic adrenal insufficiency and Addisonian crisis are given—including choice of preparation, dosage and prevention of overdosage.—*A.P.F.*

ENDOCRINE GENERAL

ACEVEDO, D.

Some tests of diagnostic endocrinology. *Actualidad Medica Peruana.* 11: 199. 1944.

A succinct epitome is offered of assay methods that are useful in all the important endocrinopathies.—*R.G.H.*

ACEVEDO, D.

Tests of carbohydrate metabolism and diagnostic endocrinology. *Actualidad Medica Peruana.* 8: 122. 1943.

The author expounds with several line diagrams the hormonal interrelationships that are involved in the control of carbohydrate metabolism as well as tests of the hormones themselves. He then discusses the diagnostic characteristics of the chief disorders that are characterized by disturbances of carbohydrate metabolism.—*R.G.H.*

BILL, A. H., AND F. M. POSEY, JR.

Pregnancy and diabetes. *Am. J. Obst. & Gynec.* 48: 405. 1944.

This report contains the statistical analysis of 44 diabetic pregnancies. The results are in general agreement with most of those of recent literature as regards fetal and maternal complications. The authors make a plea for careful study and individualization of pregnant diabetic patients. —*E.C.H.*

GONADS

ABRAMOWITZ, A. A., W. L. MONEY, M. X. ZARROW, R. V. N. TALMAGE, L. H. KLEINHOLZ, AND F. L. HISAW

Preparation, biological assay and properties of relaxin. *Endocrinol.* 34: 103. 1944.

A method for the assay of relaxin has been described. Castrated female guinea pigs were given a daily dose of 0.83 μg. of estradiol for 4 days, and a single injection of relaxin on the 5th day. Six hours following the relaxin injection, the symphysis pubis was palpated, and the percentage of animals showing relaxed pelves determined. A guinea pig unit of relaxin has been defined as that amount of hormone producing relaxation of the symphysis in two-thirds of the animals. A simple and rapid method for the extraction and preliminary purification of relaxin from sow corpora lutea has been described. Defatted luteal tissue was extracted with 2 per cent HCl, and inert material was removed by addition of NaCl to 1 molar concentration and neutralization of the extract. The relaxin was precipitated by saturation with ammonium sulphate. One mg. of the preparation, containing 15 per cent of nitrogen, represented 1 guinea pig unit of relaxin. One hundred and twenty mg. of the relaxin preparation, representing 0.12 kg. of fresh tissue and 0.5 gm., representing one-half kg. of fresh tissue, were found to be negative for estrogenic and progestational effects, respectively.—*Author's Summary.*

FLUHMAN, C. F.

The clinical use of extracts from the ovaries and of synthetic products having similar actions. *J.A.M.A.* 125: 1. 1944.

This is the first of a series of short reviews on the clinical use of endocrine preparations. It contains an excellent table of reliable commercial products which gives the amounts of the active principles they contain. The following well established indications for treatment with estrin are listed with suggestions for dosage: 1. Menopause, 2. Senile vaginitis and gonorrheal vuvovaginitis, 3. Inhibition of lactation, 4. Amenorrhea 5. Intrinsic dysmenorrhea, 6. Functional uterine bleeding, 7. periodic mastalgia 8. Induction of labor. The indications for treatment with progestin are listed as: 1. habitual or threatened abortion, 2. Functional uterine bleeding, 3. "After pains," 4. Dysmenorrhea.—*A.P.F.*

FRAME, E.G.

A micro-method for the separation of 17-ketosteroids into alpha and beta fractions. *Endocrinol.* 34: 175. 1944.

A micro method is described for the separation of urinary 17-ketosteroids into alpha and beta fractions utilizing precipitation of the beta steroids by digitonin. The method is applicable to 1- to 3-day urine collections and measures both the alpha and beta fractions. In recovery experiments the method permitted recoveries of 94 to 102 per cent of added androsterone (an alpha compound) when 1.0 to 2.0 mg. were present and of 93 to 105 per cent of added dehydroisoandrosterone (a beta compound) when 0.12 to 2.0 mg. was present.—*C.W.H.*

HELLER, C. G., AND G. B. MEYERS

The male climacteric, its symptomatology, diagnosis and treatment. *J.A.M.A.* 126: 477. 1944.

Evidence is presented that the male climacteric is a definite although not common endocrine disorder which may be distinguished by clinical and laboratory methods from psychoneurosis. Urinary gonadotropins were first shown to be elevated in functional and surgical castrates to levels not found in normal men of any age. The diagnosis of functional castration was proven by testicular biopsy. Thirty-eight patients with symptoms suggesting the climacteric were examined. Twenty-three had markedly elevated urinary gonadotropins. Testicular biopsy was done in eight and showed atrophy in all. Twenty patients were treated with testosterone and all showed improvement and relapsed when placebos were substituted. In fifteen patients with normal urinary gonadotropin excretion the symptoms were less typical of the climacteric and treatment was ineffective.—*A.P.F.*

HOENIG, E., AND M. P. WARNER.

Full term pregnancy after removal of remaining ovary at five months of gestation. *Am. J. Obst. & Gynec.* 48: 431. 1944.

A case report is presented of a normal full term pregnancy in a patient possessing only one ovary which had to be removed during the fifth month of gestation because of an ovarian cyst (10 centimeters diameter) which became twisted on its pedicle. Prophylactic oral and intramuscular progesterone was administered postoperatively. —*E.C.H.*

KESHIN, J. G. AND B. D. PINCK

Factors in male sterility. A critical review of 135 cases. *Am. J. Surg.* 66: 346. 1944.

Analysis is made of 135 sterile marriages in which the male has been examined in our clinic. Classification has been established on the basis of semen examinations. The necessity is stressed for comprehensive appraisal of all factors to evaluate properly the status of the patient for there is no necessary relationship between motility, morphology, and sperm count. Relationship between semen analyses and testicular biopsy has been considered. There is ordinarily striking correlation between these; exception occurs when total sperm count is normal but a high percentage of abnormal forms is present. Biopsy studies afford valuable diagnostic and prognostic aid. Regeneration of testicular tissue in complete azoöspermia with the final production of sperm able to induce conception has been demonstrated to be an uncommon but distinct possibility. With progressive improvement in spermatogenesis changes are noted in the type of abnormal form in a definite direction from degenerative to the type of abnormal sperm most often seen in a normal specimen. Endocrine therapy plays a limited rôle in most cases of male sterility. A simplified technic for staining spermatozoa has been described.—*Author's Summary.*